Engineering Automated systems for Pharmaceutical Manufacturing: Quality, Regulations and Business Performance

Thesis submitted for the award of Doctor of Philosophy (PhD)

Author: Diarmuid P. Meagher Bc(Hons) MEng

School of Mechanical and Manufacturing Engineering

Dublin City University

Supervisors: Professor M.S.J. Hashmi / Dr. W.G. Tuohey.

Submitted: June 2006.

Declaration

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of Doctor of Philosophy 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.

Signed: _____ Diarmuid Patrick Meagher

ID No.: 53126785

Date: 25 Sept 06

Acknowledgements

I am indebted to my Supervisors, Professor M.S.J. Hashmi and Dr. W.G. Tuohey. Great gratitude is owed to Professor Hashmi for his assistance throughout my thesis compilation and for early guidance. Likewise to Dr.Tuohey for his extremely thorough reviews of both the textual and technical material of my research, and for helping to make my thesis and papers presentable to a wider audience.

Survey research is made possible by the generous contributions of participants. I was charmed to have a group of pre-test participants who were knowledgeable in research methodology and in the area under study. Particular mention from this group is required for Fernando Cassanova at Labvantage who helped to refine the survey instrument and give encouragement to this research effort.

The 122 companies who took the time to carefully respond to the questionnaires made this research possible. Most organizations were extremely busy but still took time to respond, and oftentimes made contact to make sure that their contribution had been received. In these times, surveys are commonplace and it's easy to refuse to participate. This makes their efforts even more remarkable.

This research was conducted part time which had the potential to cause considerable strain in the author's personal life. I am blessed to have had the support, encouragement, understanding and love of my (now) wife Pippa. To her I

owe immeasurable gratitude I hope she will fully share in the value and benefits that this work will bring

Our 12 week old daughter Catherine Margaret probably knows as much about the contents of this work as the rest of my family, but they have all contributed in some way to the author's well being and drive to succeed, so credit and thanks is due to them My friends, old and new, have also played a role in the maintenance of my sanity, some portion of which was necessary to complete the work herein

This research is firstly dedicated to all people who selflessly commit to and labour for the growth of all others, those who work to remove toxic cynicism and begrudgery from their hearts and minds, and who inspire people against the odds to see the beauty in life over the ugly

Finally this work is dedicated to Pippa and Catherine My successes and heart are yours

Abstract

The pharmaceutical sector is very heavily regulated Drug safety regulations form one of the pillars of this regulation The manufacture of pharmaceuticals is carried out in an environment of onerous regulatory requirements, often from several national and international regulatory bodies The quality systems operated by drug manufacturers and their regulatory practices have an important impact on product quality The quality and regulatory requirements apply not only to handling of the medicinal products, but also to the physical and electronic systems used in the manufacture of those products, and extend to automated systems used to support quality assurance operations Design, development, building and support of such systems are ultimately the responsibility of the drug manufacturer The quality and regulatory requirements for automated systems are passed down the supply chain to suppliers In the last two decades of the 20th century there has been a proliferation in the use of computerised and automated systems for use in, or to support manufacturing Correspondingly, regulatory requirements have been imposed on the manufacturing industry This work used survey research and factor analysis to establish relationships between quality and regulatory practices, and between both quality and regulatory practices and business performance for suppliers of automated systems into the pharmaceutical market A survey instrument and an administration strategy were developed from a review of the literature It was established empirically that quality practices and regulatory practices were strongly related Specific facets of quality practices and regulatory practices were found to have had a significant impact on both market share and competitiveness expectations and also profit and sales expectations Differences in practices and performance were established for various levels of automation complexity and criticality, where criticality was a function of the risk the respondent's system posed to the manufacture of their customer's products

Publications

Accepted

Regulatory Considerations and Business Implications for Automated System Suppliers Meagher, D P Hashmi M S J and Tuohey, W G *Pharmaceutical Engineering Journal* Nov-Dec 2006

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Glossary

CMM The Capability Maturity Model of the Software Engineering Institute of Carnegie Melon University in the United States is a standard for software based on the principles put forward by Philip Crosby, the purpose of which is to increase control over an organization's software development process.

Construct The operationalising of a concept into a real measure that can be determined through an answerable question or 'item'. Several questionnaire constructs may be used to represent a variable. Several constructs may be combined into a 'factor' using factor analysis. A variable can be formed by adding the construct scores together, where those constructs form part of a factor.

Construct Validity A term that represents the logic of items that are used to capture data to represent a given variable. Good construct validity is represented by a series of measurable indicators with a sound theoretical basis for representing the parent variable.

Content Validity A term that represents how well an item represents the measure it claims to. Also called face validity.

Cronbach's Alpha A measure of internal consistency reliability used to indicate that a number of scale items vary together, and hence ultimately measure the same feature.

Design Qualification A series of activities concerning the initial user specifications of a system combined with the corresponding functional and design specifications, the purpose of which is to ensure that the system design is as intended.

EMEA The European Medicines Evaluation Agency is responsible for protection and promotion of human and animal health through the evaluation and supervision of medicines in European Union member states.

ERES Electronic Records and Signatures as defined by 21 CFR Part 11 and EU Volume 4 Annex 11.

Factor A group of constructs/items that share the same underlying variance. A factor can be used to produce a single variable representative of all the constructs within that factor (See glossary entry for Construct).

FDA Food and Drug Administration of the Unit States Department of Health and Human Services that regulates *inter alia* the testing, approval and manufacture of drugs for human use.

GAMP Good Automated Manufacturing Practices as described by the International Society of Pharmaceutical Engineering.

GMP Good Manufacturing Practices, the rules as set out by national and international bodies for the manufacture of *inter alia* medicinal products Sometimes called Current or cGMPs

ICH The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use are a worldwide body supported by the FDA and the European regulatory agencies for provision of global common guidelines for the manufacture and control of drugs

ISPE The International Society for Pharmaceutical Engineering, a professional body that gives guidance to the pharmaceutical manufacturing world on pharmaceutical technology and regulatory compliance Responsible for production of the GAMP guide

Part 11 21 Code of Federal Regulations Part 11, is the FDA regulation for using electronic records and signatures in a Good Manufacturing Practice environment

PAT Process Analytical Technology is an initiative from the FDA focused on allowing manufacturers to use the most advanced measurement and quality system techniques for controlling their processes, based on scientific approach and risk management

PIC/S The Pharmaceutical Inspection Convention and the Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S) are two bodies that include 27 European and Oceanic countries, whose focus is to provide cooperation in Good Manufacturing Practice matters

Predicate Rules A mainly American term for the set of Good Manufacturing Practice and Quality System regulations relating to a given regulated industry

Principal Components Analysis (PCA) A branch of factor analysis used to find a reduced number of underlying factors, or components, out of a large number of components

Quality Assurance The set of activities and processes in an organisation that aim to ensure that standards of quality are being met

Quality Control An set of activities, usually consisting of inspection of product, designed to ensure that specifications have been met

Questionnaire item An item on a questionnaire which can be operationalised constructs to represent variables, or can be open qualitative questions

Software Development Life Cycle (SDLC) An approach to software development whereby software is specified, built and tested in a continuous iterative system of investigation of requirements, analysis, design, testing and continual maintenance over the complete life of a software project Several models exist, each of which describe a variety of tasks that takes place during the complete lifecycle of a software product

System Compliance A characteristic of a system whereby all of its elements and functionality conforms to standards which includes regulatory standards

System Qualification / Validation A series of activities aimed at providing objective evidence that the system is fit for it's intended and specified purpose

TQM Total Quality Management is a management philosophy that has total involvement of every employee in a company in quality related activities at its core

Validation The set of activities concerned with proving that a system is suitable for its intended purpose

Variable A concept that can be measured and assigned a score In survey research, this can be derived from constructs (See glossary entry for construct)

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Chapter 1 Introduction

The pharmaceutical industry operates in a climate of onerous governmental regulation Regulations concern three main areas, product quality, price and marketing The vast majority of pharmaceuticals in the world are produced by an oligopolistic group regulated by the Food and Drug Administration (FDA) of the United States, or the European Medicines Evaluation Agency (EMEA) of the European Union An internationally supported body, the Pharmaceutical Inspection Co-operation scheme (PIC/S) produces regulations that are aligned to the EMEA regulations [1] It has wide membership from both the European Union members, and from non-EU members such as Australia, Canada, Malaysia and Singapore The World Health Organization also provide minimum, less onerous directions for quality in drug manufacture although these are guidelines rather than legal requirements [2] Initiatives such as that of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) have created common guidelines for worldwide development and production of drugs, which draw on both the European and US rules [3]

Manufacturing and related systems are an important factor in drug product quality Technological innovation has meant increased emphasis on computerization and automation of processes This has resulted in additional concerns for product quality and consequently increased regulatory requirements for such systems This work

focuses on those systems Quality requirements for both manufacturers and system developers have increased in line with the complexity of the technology

The design, development and production of automated systems for pharmaceutical manufacture must adhere to the regulations imposed upon the drug manufacturer for whom those systems are intended These regulations have become increasingly rigorous and rigid over time due to a process labelled by some as 'regulatory creep' or 'regulatory spiral' [4] - [6] Of course, genuine concern for product quality is the main reason for the ever-evolving litany of regulatory requirements [4] Vendors and developers providing for any market must be able to meet their customer's requirements Regulatory compliance and high quality are requirements for pharmaceutical systems

In biopharmaceutical and pharmaceutical manufacture, validation requirements for processes and critical systems that can affect drug quality are substantial [7] The regulatory agencies have contributed to additional engineering requirements that systems must comply with in order to support validation The requirements for manufacturing plants and systems have grown and have pervaded the lifecycle of their systems These are mainly in the form of hardware and software design requirements and system validation requirements Vendors into these industries must be able to support these two requirements, *evidential* design for purpose and validation

For control systems used in manufacture, it is difficult and often impossible to delineate between systems that provide management of critical systems and those which are non-critical [7] This very often leads to an extension of effort beyond known critical systems to ensure that no potentially critical components are missed, when deciding where the regulations are applicable The requirement for systems to be fully verifiable from their initial specification to retirement means that every aspect of their specification, design, development, installation, commissioning, validation, and operating phases must be documented in an acceptable manner to both the manufacturer and ultimately the regulator

The use of vendors in the compliance process is advocated widely [7] – [10] Some commentators even recommend that manufacturers should consider using suppliers that provide full turnkey packages that include all the documentation and validation requirements This can be a very efficient means of bringing a new design and build project to a swift conclusion, by completely combining the engineering effort with the regulatory compliance effort

There is a huge array of automated and computerized systems that are deemed either directly or indirectly critical to the quality of the drug being manufactured These include measuring systems, information systems and process control systems Software can either be embedded in those systems or exist on magnetic media on computers or computer infrastructures The quality requirements for such software are heavily scrutinized and prescribed by the regulators The scope of this

research is those automated and computerized systems produced to operate under good manufacturing practice regulations set out by the FDA, EMEA and consequently by the PIC/S

This research focuses broadly on the manufacture of finished pharmaceuticals and biopharmaceuticals for human use as specified in the FDA regulations and the EC directives It hence precludes medical devices and bulk pharmaceuticals not requiring compliance to these regulations Over 80% of world Pharmaceuticals are manufactured in countries covered by FDA or EMEA/PIC/S regulations [4]

Systems supplied to both the pharmaceutical and biopharmaceutical manufacturing industries are relevant to this study, and for the purposes of this study pharmaceutical can be taken to mean biopharmaceutical also

Substantial evidence exists from the literature of the positive relationship between manufacturing quality practice and organizational performance, some of which is presented in this work There is apparently no evidence in the literature of whether developers, designers and vendors of systems for the pharmaceutical manufacturing industry, with its strong regulatory focus and uptake of regulatory related practices, have mined a similar vein of business success

This work aims to determine the relationships between regulatory focus and practices, general quality focus and practices, and business performance for system

developers of automated and computerized pharmaceutical manufacturing systems The literature review looked at the trends in the regulations, specific regulatory requirements, quality systems, and the effects of quality system practices in general on business performance

A survey instrument was designed and administered to a sampling frame based on the *Pharmaceutical Technology* journal 'Buyers guide' [11], an internationally focused guide purporting to include 80% of all technology suppliers to the Pharmaceutical industry *Pharmaceutical Technology* has both European and US editions This claim was validated whilst building the database by using other databases and by performing Internet trawls Through following standard accepted methodologies for questionnaire design and development, threats to validity were avoided in advance Variables were selected and grouped into quality practice variables, regulatory practice variables and business performance variables Constructs were generated to accurately capture data that reflected the variables The instrument used a series of Likert scale items and closed type questions to determine data for quality practices, regulatory practices and business performance The instrument was administered by electronic mail after receiving permission from the respondents and conducting both pre testing and pilot testing Factor analysis was used as the basis for establishing reliable summated scales from the data Analysis and hypothesis testing was conducted using SPSS software employing correlation and difference testing, factor analysis and stepwise regression analysis [12]

From a regulatory perspective several things were considered The FDA and EMEA pharmaceutical regulations themselves were important Focus and adherence to regulations were determined from survey results The Good Automated Manufacturing Practice guide (GAMP) from the International Society of Pharmaceutical Engineering (ISPE) [13] has now become a *de-facto* standard for selection and production of automated equipment for pharmaceuticals and pervades both the European and FDA requirements It was assessed whether there was a relationship between business success and regulatory activities such as the application of this guidance by providers An important regulatory support requirement is the provision of adequate design documentation and validation support for end user verification that the systems delivered meet their intended purpose Relationships between the extent of this practice by suppliers and business performance were also determined

Total Quality Management (TQM), the ISO 9000 quality series, and the Software Engineering Institutes Capability Maturity Model (SEI CMM) [14] for software quality are important systems for establishment and improvement of quality performance in software development environments It has to be recognized that although suppliers may not subscribe to formal systems or guidelines such as ISO, the CMM, GAMP and TQM they may still be engaging in such bespoke practices as to be at least functioning in a manner equivalent to those systems To this end, it was important to derive a set of fundamental quality constructs common to all these systems In this

research, those constructs were derived from a literature review and analysis of the core criteria specified in the literature, ISO, CMM, GAMP, TQM, the US Malcolm Baldrige National Quality Award (MBNQA) [15] and the European Quality Award (EQA) [16] Business performance constructs were selected from a review of the MBNQA criteria for performance measurement and from a review of the wider literature on performance measurement While recognizing that quality or regulatory practices are not static, it was possible to examine multivariate relationships between current practices and business performance, and to establish cross-sectional deductions using empirical and analytical methodologies

This study is intended to be useful in several respects It provides guidance to developers of computerized and automated systems for use in pharmaceutical manufacture as to best (or optimal) quality and regulatory practices It could also give manufacturers, regulators and professional industry bodies indications as to how well developers perform with respect to quality system practices and regulatory compliance To the wider quality profession, it would provide insight into the extent to which commonly held relationships apply within this specialised sector

At the time of writing, the author has spent 8 years working in the pharmaceutical and medical device industries as a Process Engineer, Validation Engineer, Quality Engineer and an engineering compliance Consultant Over this time sea changes in regulatory and quality practices have been observed Categorizing the business effects of revolutionised practices was a motivation for this research

The remainder of this introduction summarises the study background, quality management systems, pharmaceutical regulations, the aims and hypotheses of the research, and the methods used to acquire data pertaining to, and for testing the hypotheses

1 1 Background

Product safety regulations affect the physical manufacture of drugs more than the other two regulatory factors (marketing or price) [4]

Fundamental to all product quality regulations are the employment of Good Manufacturing Practices (GMPs) and 'current' Good Manufacturing Practices (cGMPs) It is within these that the requirements are laid out for the production of medicines for human consumption The GMPs of both the US and Europe provide basic requirements for equipment and computerized systems used for pharmaceutical manufacture Whilst the requirements for cleanability and maintenance of physical equipment are easily understood and applied, those for the automation of processes are more complex Systems must comply with those requirements to allow their employment in medicinal manufacture and hence developers must adapt to them and their application

Automation and computerization of processes results in significant process advantages and economies and if designed correctly can serve to enhance GMPs [17]

It is acknowledged that quality must not only be built into the drug but must also be built into any system associated with the product [18] Validation is the means by which the manufacturer must verify suitability for purpose, and the system design must be implemented in a way that it can be validated The systems should be designed so that validation does not show up any inherent GMP weaknesses and that it is hence suitable for its intended purpose Qualified or validated equipment is a fundamental component in GMP In order for validation to be successful, validation features need to be built into equipment GMP design problems, and validation activities to ensure that those problems have been eliminated, should be identified at design evaluation [19][20]

When regulatory compliance requirements are considered for implementation into a system for use in a GMP environment, the level of detail and complexity rises This can cause a substantial increase in the time taken to select, design, acquire, build and install the system The complexity of equipment for use in GMP environments can vary greatly from that used in non-GMP environments for a given purpose [21]

The level of detail of documentation required by differing manufacturers from vendors varies So do vendor attitudes (and costs) towards providing documentation

to the extent required by the industry There are often disputes between vendors and manufacturers over provision of validation documentation This can result in further unanticipated demands for payment from the system vendors, and other conflicts in expectations A greater emphasis on regulatory issues results in better and more complete equipment, which will be better understood by everyone involved and produces fewer misunderstandings between vendors and manufacturers [21]

Quality is important for both the drug manufacturer and the manufacturing system developer It is desirable for the developer to produce high quality goods in an efficient and competitive environment This must be demonstrable to the drug manufacturer Hence, it is postulated in this thesis that quality practices, and practice directly linked to regulatory requirements or guidelines, enhance business performance It is also put forward that quality and regulatory practices are mutually dependent in an organization producing automated goods for the pharmaceutical market

Adherence to the regulations by both manufacturers and system developers is achieved mainly through quality management systems Sharp [5] argues that there is a 'spiral staircase' effect evident in the relationships between medicine manufacturers and the regulators He explains that on quality issues it is sometimes the regulators who lead and other times it is the manufacturers When the regulator leads, the manufacturer interprets the regulations more tightly than required to ensure compliance and hence takes over the lead, as their position becomes the

expected position The regulator responds by tightening the regulations to match industry practice and expectations, taking over the lead, again Manufacturers often then take the lead by introducing new technologies which the regulator must make rules for (as in the case of Process Analytical Technology [22] and 21 CFR Part 11 [23]), and so on The net effect of this is an overall spiralling and tightening of the regulatory and hence quality requirements with time for the manufacture of goods

Sharp [5] says that quality assurance consists of all those activities that involve GMP and Quality Control In discussing the functions within a pharmaceutical manufacturing environment, he says that engineers need to be fully appraised of the special requirements for medicines manufacture A test of validity for any quality effort in pharmaceuticals is that if that effort does not ultimately contribute to patient well being then it is unnecessary expense Deciding on what does or does not contribute to wellbeing can be a difficult job for engineers, particularly when the manufacturer themselves are unclear However, when software is used to support GMP activities, then the GMP quality assurance requirements apply to the software Standard Software quality assurance philosophies and methods can be invoked to help fulfil the regulatory requirements for software quality

With time, vendors and manufacturers have been developing better partnerships when designing systems for regulated environments Validation and documentation are seen by some vendors as necessary, fundamental components of the products

they are selling Examples also exist of systems that have been developed for industry by several manufacturers in conjunction with several vendors [24]

The onerous requirements that suppliers must adhere to if they wish to be competitive in the industry have resulted in quality requirements for software vendors far beyond what is normal in software engineering [25] An example of this is where requests for complete documentation of the software development life cycle from manufacturers are made of the vendors, vendors have to spend much time preparing documentation to a standard determined by the customer, and must deliver it together with the software product The increased involvement by the regulators in software quality assurance is seen as both a complicating factor and a positive influence on the development of software for the pharmaceutical industry This research is heavily concerned with those software quality assurance practices employed by developers, as software quality is fundamental to the quality of automated and computerized systems

The gaps that may exist in regulatory awareness by developers may be due in part to lack of training in educational institutions for engineers designing systems for use in GMP environments Engineers should have greater access to training on pharmaceutical issues [26] including regulatory matters [27]

In this work, quality and regulatory practices and business performance were measured The additional element of regulatory focus in a quality system for

developers of automated systems for the pharmaceutical industry could be seen as making quality a more important business factor for that industry than for other industries This would become clear from the survey analysis The effects of the additional regulatory element in supplier practices were determined and compared with the established relationships between quality practices and performance in the literature for other sectors [28]-[31]

The differences in the nature of the questions asked in this work from those in the literature are reflected in the survey design Criteria and questions from the literature are developed regarding quality practice and business performance for application in an automated system / software vendor setting Criteria representing regulatory factors were deduced from the themes and considerations in the literature, although no evidence exists of survey research that uses regulatory constructs relevant to this work The literature on regulatory influences on business performance tends to look at performance of companies subject to regulation (such as electricity companies), rather than looking at their actual regulatory practices

1 2 Quality Management

The importance of quality management system implementation is well documented Quality management exists in many forms The most common and influential systems of quality management include systems for Total Quality Management (TQM), the ISO 9000 series of quality management systems and for software the

Capability Maturity Model (CMM) [14] These systems are discussed later, and their fundamental features were used to develop constructs for quality practice measures

Customers of engineering companies want evidence that product quality is being improved, whilst at the same time requiring competitive product prices [29] This means that quality management efforts must improve both processes efficiencies and the end product itself Engineering firms are expected by their clients to be taken along with the tide of the quality revolution the same as any other firm Many firms see the advantages of having high quality management standards and there has been an increase in the percentage of small companies going for quality awards such as the Malcolm Baldridge National Quality Award (MBNQA) [15] in the United States and the EQA [16] in Europe

1 3 Pharmaceutical Regulation

Many regulatory requirements may be met by excellent quality management practices on the system developer's side Essentially, regulatory requirements consist of a set of instructions to manufacturers regarding their quality systems and processes Evaluation of both quality management and regulatory factors provides a balanced assessment of the overall quality effort actively exercised

Applying the principles of quality management to the design of automated systems makes sound business sense as well as assisting with regulatory compliance [32] It

allows the full potential of those systems to be realised, as it is universally realised that better business performance is related to quality However, no relationship seems to have been established in the literature between regulatory compliance and business performance, or between quality practices and regulatory compliance This is the case for the sector being studied (and could be applied to other sectors)

The US regulators are generally seen as rule-makers when it comes to regulation whereas the EU are considered more consensus based when resolving regulatory matters [4], making much less use of courtrooms to solve disputes or for taking punitive action 'Regulatory clout' holds for both regions though It is recognised that regulatory change can arise from changes in competitive structures and markets, rather than just from product safety or economic events Hancher [4] sees competitive factors as being greater than drug safety factors in the strength and flexibility of drug regulation The concept of regulatory conservatism is often the result of fear of wrong decisions being made, leading to increasingly onerous requirements for product safety and hence equipment design and validation

Validation costs have increased in part due to uncertainty about regulatory requirements [33] The trend for validation of processes in pharmaceutical manufacture has been to validate right back from the front end (finished product end) of the process to the facility support utilities, such as water and air conditioning systems

Christoffersen and Jespersen [34] point out the importance of QA in all aspects of pharmaceutical projects from conception to completion Particular importance is given to the acquisition and management of documentation throughout the project to ensure that both customer and regulatory requirements are met This has both cost and organizational consequences for the system developer as they must be able to provide documentation that reflects the specification, design and testing of their systems

Andrews [35] says that the challenge that the pharmaceutical industry must meet is maintaining the balance between increased use of automation to reduce business costs and maintaining regulatory compliance, which is costly Failure to adequately validate has resulted in many "observations" and warning letters to manufacturers by the FDA The FDA has acknowledged that computers and their validation are compliance risks and that rises in non-compliance as a result of increased computerization have accrued [36]

Certain regulations have had substantial impact on the requirements for systems used for pharmaceutical manufacture, not least the FDA's 21 CFR part 11 [23] (known as 'Part 11' in the industry), and EU volume 4 annex 11 [37] These rules set out requirements for computerized systems and in particular for electronic record keeping Good engineering practices supplemented by guidance from the regulators and industry bodies such as the Good Automated Manufacturing Practice (GAMP)

[13] initiative has evolved to support regulatory compliance These specific regulations, guidance and their effects are discussed in the literature review

1 4 Aims and Hypotheses

The aims of the study were to assess the relationships between quality practices and regulatory related practices, between quality practices and business performance and between regulatory practices and business performance for developers of computerized and automated systems for use in pharmaceutical manufacture through survey research Research questions focus mainly on the quality and regulatory features of the aforementioned computerization and automation Hence this distinguishes between other regulatory related factors such as cleanability or product contact material concerns The regulatory focus is thus constrained to those hardware and software automation elements that make up a system for use in pharmaceutical manufacture

This research aimed to use the results obtained from the survey questionnaire to evaluate the relationships between practice and performance for the defined variables, which are obtained from the literature or introduced for the purposes of the study It aims to address a current gap in the literature regarding the quantitative empirical evaluation of the relationships between regulatory practices, quality management practices and business performance for system developers supplying the pharmaceutical manufacturing industry

The following hypotheses were tested

H1 High levels of quality systems implementation for developers of automated and computerized systems for pharmaceutical manufacture result in better business performance

H2 Firms with higher general quality implementation levels have a better regulatory focus

H3 High levels of regulatory practice results in improved business performance

The relationships established for H1 have been established for many other sectors and are widely accepted as valid across other industries, but have not been established for suppliers of automated solutions to the pharmaceutical industry Due to the hypothesised interactions between regulatory practices and quality practices, it was postulated that this relationship needed to be established for the pharmaceutical sector, as the regulations could be seen as a complicating factor This might have meant that the generally accepted relationship between quality and business performance may not have held here There was no evidence in the literature concerning the relationships H2 or H3

1 5 Methodology

System developers selected from the other major pharmaceutical engineering industrial journal from the International Society of Pharmaceutical Engineering (ISPE), *Pharmaceutical Engineering* [38] were used to validate the 'Buyer's guide' selection [11] Questionnaire constructs were developed in accordance with the literature on survey research

The data was tested for reliability using accepted standard methodology Factor analysis was used to establish reliable scales and multiple regression models were used to test for relationships and hence to try to disprove the research hypotheses SPSS software [12] was used to handle the raw survey data and produce useful statistical results

1 6 Summary of Introduction

System developers producing for the pharmaceutical manufacturing industry must be capable of producing high quality automated and computerized products that comply with strict regulatory requirements The quality and regulatory practices employed by those developers may have an influence on business performance, and on each other This study set out to empirically evaluate these relationships and hence address a gap in the literature An overview of quality systems, regulations and their effects, and the research methodology has been provided The research hypotheses have been presented

Chapter 2 Literature review and derivation of study variables.

2 1 Development of computerized and automated pharmaceutical manufacturing systems

Uzzaman [39] states that compliance with Computer Systems Validation (CSV) regulations should be a by-product of good systems engineering practices designed to optimise return in investment Therefore, by adopting good engineering practices, it should be possible to achieve two objectives, regulatory compliance and an efficiently produced quality product A good quality approach aimed at best practice can go a long way to achieving compliance However, good engineering practice on its own is unlikely to result in compliance Developers should be mindful of the specific regulations in existence such as 21 CFR Part 11[23] from the FDA

Margetts [40] says that attention must be given to the following 13 points when considering the suitability of computerized systems for use in pharmaceutical manufacturing These points ultimately lead to high quality systems and regulatory compliance

1 Validation
2 System description
3 Staff qualifications
4 Quality system under which software is developed

5 Study of the installation environment

6 Security

7 Built in checks for critical data entries and control over alteration

8 Input and output accuracy tests

9 Structural testing of the software

10 Functional testing of structurally sound software

11 Change control procedures

12 Data backup and restore procedures

13 Contract procedures for use of external personnel

Margetts does not mention provision of documentation as one of his 13 points, which is generally a crucial requirement

Standards such as the Capability Maturity Model (CMM) [14] and both IEEE 1074 [41] and ISO 12207 [42] software development life cycle standards should be considered when adopting best practices in a design environment [39] The quality requirements for pharmaceutical manufacturing Computer Systems Validation (CSV) exceed those provided by ISO 9000 and 'TickIT' [43] accreditation according to Wingate [44] Other industrial engineering standards should be considered when designing systems with validation for use in a pharmaceutical environment in mind such as the SP88 model, which is a pre-cursor to the Instrumentation Society of America's (ISA's) S88 model [45][46]

In the last 25 years (pre 2000) there have been significant changes in the design of equipment for pharmaceutical manufacture [5] Primarily there has been a move away from borrowing from other industries such as food towards a position where bespoke systems are manufactured with GMP principles considered Anyone who is involved with the development of a computer system for use in a GMP environment is responsible for its validation and regulatory compliance [8][25][47]

In the 1970's the concept and initial regulatory rulings on validation of processes and manufacturing systems including automated systems was introduced [48] Further concerns over the increasing use of computers in all areas of pharmaceuticals through the 1980s and 1990s led to further validation guides and pressure being applied to the FDA to make increased and definitive ruling on the subject They did so in the form of 21 CFR Part 11

Carrier [9] recognizes a trend with suppliers in that they have made considerable investment into trying to understand the 21 CFR Part 11 rule for electronic records, and that they are building their product functionality based on the rule It is suggested that this is done to become compliant and to create a competitive advantage through product differentiation over competitors Carrier does not consider though, that the supplier might create an impression that compliance is *required* for their product, when it may not be within the intended scope of 21 CFR Part 11

Often, systems that are used for other industries cannot be used in a GMP environment due to compliance requirements [49] Direct investment in the rule can thus benefit both the industry and suppliers so that suppliers should be able to knowledgably discuss the rule with manufacturers One requirement of developing Part 11 compliant systems is to ensure that adequate documentation is available from the vendor explaining all the design permutations and revisions of any software involved This requirement of the rule may have the effect of putting more onerous documentation practice expectations on developers than they were used to prior to the ruling, or when developing systems for other industries This would require quality system inputs for the maintenance of development and revision records, which are auditable by manufacturers

The increased amount of automation in pharmaceutical manufacturing, storage and distribution has increased the potential risk to the medicinal product [50], as well as mitigating the risks associated with human error This has led to the proliferation of rules and industry guidance on the use of such systems Automation can be built as a modular system at the developer's site or be part of the production plant's distributed automation solution Either way, external system developers may be used in building the systems The quality and regulatory practices for each of these developer categories are relevant

Wingate [48] states that regulator's expectations have increased in line with manufacturer capabilities This is not strictly accurate in the case of 21 CFR Part 11,

where manufacturers did not necessarily have the capability to comply These expectations are then passed on to suppliers A problem with this is that the GMPs can be interpreted differently and do not provide detailed guidance, which naturally leads to differences in compliance strategies

Validation has existed in the software engineering world in a different sense to that required by the pharmaceutical industry [51] In many software projects, outside of safety or mission critical contexts, validation has often meant checking that software works after it has been developed The validation required by regulators is broader in scope, and starts much earlier in the design and development process, at the specification stage It also extends forward into the operation of the system by the end user

Best practices in design, development and validation as viewed by pharmaceutical manufacturers have not always been followed traditionally by software vendors Although in software terms, the requirements from manufacturers are not much different from other industries, the interpretation and integration of the GMPs into the software product is novel The difficulties associated with applying the GMPs to software makes assuring compliance onerous

The demands placed on developers by the pharmaceutical industry are no different than what is expected by any industry, in that software should work as specified and should be proven to do so The expectations of the FDA are not that far removed

from what is required in normal industry for established good software engineering practices The FDA has stated in the past that they do not intend to establish new standards for development of software and have pointed to industry standards such as ANSI and IEEE [51]

With regard to computer system regulatory compliance, computer hardware needs to be considered as well as software According to the FDA's compliance policy guide 7132a 11 [52], when computers are used to fulfil GMP related functionality hardware is viewed as equipment as defined in the GMPs This equipment will hence require the same level of controls applied as for other equipment under the remit of the regulations

The involvement of vendors in the software development life cycle can be intense The vendor must be able to fit into the manufacturer's life cycle model and provide all the documentation and design features necessary to support it Each aspect of the software firm's design process must be verified by both the firm itself and by the manufacturer Some of this verification occurs through factory testing and verification and some as site acceptance and final testing at the pharmaceutical manufacturer's site

Design Qualification (DQ) is the process of building a set of requirements and specifications for a system to be developed for a pharmaceutical manufacturer In response to the design requirements of the manufacturer, the vendor will produce a

set of detailed design specifications The combination of these reviewed specifications and the original requirements make up the DQ It requires that the design is in compliance with GMPs and this should be demonstrable as stated by Annex 15 of the EC working party on Control of Medicines and Inspections [53] The ICH Q7A guide [3] says that design review should be used to ensure that the systems are suitable for their intended purpose In practice the design review and DQ are carried out by the system purchaser, acting on behalf of the eventual end user As this determines the eventual suitability of systems for implementation based on *inter alia* their compliance to GMPs, then there is pressure on the developer/vendor to ensure compliance Ultimately compliance is up to the manufacturer, so the interface between developers and the manufacturers is an important one

It may be possible to attain a similar or better standard than adherence to GAMP produces by following other established industry development guidelines such as the Capability Maturity Model (CMM) [14] from the Software Engineering Institute according to Foote [54] However, the requirements for working to the CMM differ from those required by GAMP so it is not obvious that they produce comparable performance when each is adhered to independently Use of industry established industry standards as suggested by Foote may not result in full compliance In particular, suppliers would not be used to the language used by the regulators, or the expectations from regulators for documentation standards, if the CMM is relied on solely

Suppliers can often lose out on opportunities because they are unaware of requirements for the software they produce in terms of validation and regulations, although they are capable of meeting those requirements within their current organisational structures Similarly, manufacturers may lose out, as they may not necessarily be choosing the best software developers, merely the more regulatory aware ones

2 1 1 Food and Drug Administration regulations

The FDA guidelines on process validation [55] are not legal requirements (unlike the regulations themselves) but the FDA deems its principles acceptable for pharmaceutical manufacture and fit to aid compliance with the regulations Process validation includes verifying that equipment is suitable for its intended purpose The guidelines define the basic principles of quality assurance in terms of medicinal manufacture as follows

1 Quality, safety, and effectiveness must be designed and built into the medicinal product
2 Quality cannot be inspected or tested into the medicinal product
3 Each step of the manufacturing process must be controlled to maximise the probability that the finished medicinal product meets all quality and design specifications

The term medicinal is used here to differentiate between the drug product and the software product Systems have a role in meeting these requirements and must be capable of supporting them The process design and validation is important for achieving these quality assurance aims In determining validation requirements the FDA urges manufacturers to consider any factors that might affect product quality including equipment functions Validation should examine the design of equipment used in, or in support of the process The process validation guidance tells manufacturers not to rely solely on vendors when choosing equipment, which means scrutinising the vendors design and quality practices

If a computer related system is performing a cGMP related function then software is deemed to be a record and hardware falls under the 'equipment' tag in the regulations [53] Software that falls under this category includes applications that perform process control, laboratory analyses, and acquisition, storage and processing of data required by the GMPs

The instructions, procedures and specifications stored as programme source code used in computer applications with cGMP impact are deemed to be equivalent to their paper equivalents in a manual system The FDA requires that source code is made available for review and approval by the manufacturers [56] This puts an onus on the designer for that code to be readable In fact, the FDA considers source code and its supporting documentation for systems used in process control to be part of

the master production and control records This code must hence adhere to the same requirements for master production records as outlined in the predicate rules for control of manual records

In the US, the responsibilities of vendors of software applications to the pharmaceutical industry mean that they may be liable to prosecution if their product leads to adulterated or misbranded drugs finding their way on to the market as a result of vendor negligence [57]

FDA 21 CFR Parts 210 [58] and 211 [59] give the requirements for Good Manufacturing Practice (GMP) for finished pharmaceuticals Part 210 gives general requirements for the manufacture of drugs whilst Part 211 is specific to the manufacture of finished pharmaceuticals Part 210 gives the legal standpoint, applicability and definitions used by the FDA in the GMP regulations Part 211 details the requirements for automatic, mechanical and electronic equipment These equipment requirements can be summarised as follows

(a) Such equipment including computer related systems should perform functions satisfactorily It should be calibrated routinely, inspected and checked regularly according to a written plan for doing so
(b) For computer related systems, adequate controls should exist to ensure that only authorised persons institute changes to batch records Inputs, outputs and

algorithms should be checked for accuracy Backup data should be maintained for data and programs

The inputs and outputs from a computer system should be regularly checked for accuracy and the expected responses verified [59] This means that they must be designed in such a manner as to allow this to happen Built in controls may be used to determine the frequency and extent of such testing

2 1 1 1 FDA rule 21 CFR Part 11 – Electronic Records and Signatures

One of the most crucial regulatory changes with regard to electronic systems and computers has been the introduction of 21 CFR Part 11 [23] in 1997 It was not enforced until 2000/2001 It makes up a substantial part of the regulations that must be adhered to by developers of systems into the pharmaceutical industry The rule has been interpreted in various ways and it has never been clear whether the more rigid interpretations have been propagated by vendors looking for a competitive edge, by using scare tactics regarding the scope of the rule 21 CFR Part 11 is the FDA regulation concerning the equivalence of Electronic Records and Electronic Signatures to paper records in the pharmaceutical industry Its scope is *inter alia* pharmaceutical manufacture The purpose of Part 11 is to allow the use of electronic records in lieu of paper records and electronic signatures in lieu of written signatures, as long as the requirements of the predicate GMP rules are still met The regulation applies to electronic records that are created, modified, maintained,

archived, retrieved or transmitted, should those records be required under those same predicate rules The regulation means that all computer hardware, software and associated documentation must be available for inspection by the agency where the related system handles records required by the predicate rules

Part 11 requires system controls and procedures which must ensure that

(a) Systems are validated to ensure 'accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records'

(b) The controls and procedures should allow records to be generated which are human readable and are fully representative of the record that was initially created

(c) Records are protected for a sufficient timeframe dictated by the predicate rules to allow their retrieval for inspection

(d) Access is limited to authorised personnel

(e) Audit trails should be built in to track all changes and the history of records

(f) Checks are carried out to ensure that only authorised people can access and use the system at the level assigned to them (e g to sign, approve, or to initiate automated sequences in a process)

(g) Checks are carried out to ensure validity of data at the point of entry

(h) Personnel are trained appropriately

(i) People accept the accountability of their signatures in the same way as they accept the integrity of a written signature

(j) Appropriate documentation handling procedures such as revision change control, distribution and access control for any documentation involved

The controls required to ensure the security and integrity of electronic signatures are detailed In summary they are

(a) Password and identification codes should be unique combinations
(b) Passwords and identification codes should be revised periodically
(c) Procedures should exist for lost, stolen or otherwise compromised passwords and for identification code generation devices

The introduction of Part 11 resulted in many reservations, difficulties and complaints from industry as to the cost and complexity of compliance [60][61], even with published guidance from the FDA and industry bodies aimed at helping developers to comply [62]

The use of clear requirements specifications by the manufacturer when acquiring technology is of paramount importance and should include requirements for compliance with Part 11 This compliance may be assessed in the form of vendor audits or questionnaires, so it is clearly in the supplier's interest to be ahead of the game

The ISPE guide for complying with the rule details 19 technological requirements that are supplier responsibilities (in that supplier involvement is required in order to ensure compliance with those requirements) [62] The remainder of the requirements of the rule can be met by procedural means at the manufacturer's site or through on site validation One procedural requirement for suppliers is that they must be able to demonstrate that personnel involved in the development of compliant systems have appropriate education, training and experience [23]

The array of technological features required for compliance with Part 11 is hence produced in table 2 1 1 1 1

Table 2 1 1 1 1 Technological requirements of 21 CFR Part 11 – Supplier responsibilities [62]

Requirement number	Related clause in 21 CFR Part 11	Requirement
1	11 10 (a)	Systems must be able to detect invalid or altered records Systems must have a searchable audit trail which can track alterations to records
2	11 10 (b)	It should be possible to access electronic records and present them in human readable form
3	11 10 (b)	It should be possible to electronically export records and associated data (such as audit trails) from the system of interest
4	11 10 (c)	Systems should be able to maintain electronic records and associated data over the period that paper records would be required, despite upgrades to that system or its operating environment
5	11 10 (d)	System access should be restricted in accordance with pre-determined rules

Requirement number	Related clause in 21 CFR Part 11	Requirement
6	11 10 (e)	Systems should be capable of recording all record create, update and delete operations Updates should not write over previous data Data must be stamped with the time, data, and originator of the creation, update or deletion Alteration of the records should only be possible by authorised personnel
7	11 10 (f)	Where sequential operations are required, the system should only allow authorised sequences to be performed
8	11 10 (g)	The use of defined functions and features should be restricted to authorised personnel in accordance with configurable rules Changes to restrictions should be captured by the system
9	11 10 (h)	Where devices are required to act as data or command sources, the system should enforce this requirement
10	11 10 (k)	Where the documentation for the system is electronic and can be changed by the manufacturer, changes must be captured in the audit trail
11	11 50	Where electronic signatures are used they should contain at a minimum, the name of the signer, date and time of signature, and the meaning of the signature (e g approve, review) The components of an electronic signature are subject to the same controls as other electronic records
12	11 70	The system must provide a method for linking signatures to records in a way that prevents the signature from being removed, copied or changed for use with any other record
13	11 100 (a)	The system should enforce uniqueness of the electronic signature and prevent reuse in any form It should not be possible to delete information relating to a signature from a system
14	11 200 (a) (1)	Non-biometric signatures should have at least two distinct components
15	11 200 (a) (1)	If system usage sessions are not continuous (if the system is left alone for a defined period), then rules should exist for re-entry that requires two components of identification (e g user name and password)
16	11 200 (a) (1)	The system should ensure that two identifying components are used on first signing in to the system and after a break in a usage session

Requirement number	Related clause in 21 CFR Part 11	Requirement
17	11 200 (a) (3)	Electronic signature information should not be accessible by ordinary means (i e by any reasonable means)
18	11 300 (b)	Systems should require passwords to be changed periodically although it is recognised that for some embedded or PLC based systems this may not be possible and procedural controls may be used
19	11 300 (d)	Systems should log attempts for unauthorised access and should take action if continuous failed attempts are made (such as locking itself out)

It is important to understand the origins of Part 11 in order to be fully able to evaluate its effects, application, and the upheaval it has caused in system development

The rules on record keeping and the use of signatures in pharmaceutical manufacturing are detailed in the predicate rules Records are required to be maintained for a variety of functions in pharmaceutical manufacture 21 CFR 211 [59] details the record requirements Specifically these are

1 Equipment cleaning, use and maintenance records (Calibration records and inspection records are required to be maintained)
2 Component, drug product container, closure and labelling records
3 Master production and control records (batch to batch monitoring of products) including the instructions and specifications necessary to manufacture
4 Batch (specific) production and control records including process measurements
5 Laboratory Records including methods and result data and analysis

6 Distribution Records

7 Customer complaints

Other requirements for maintaining records are included in Part 211 and are implicit in other criteria For example, validation data for automatic, mechanical and electronic equipment and program backups are required to be maintained Many technologies are employed in the industry, which use computers to store and handle records for all the items above Many of the records, such as customer complaints and distribution records are often managed on manufacturer designed and built applications However, many of the control and acquisition records are stored on vendor-developed systems outside of the manufacturer's direct environment Typical of these might be chromatography data systems for laboratories which usually use off the shelf software packages, or PLC controlled vendor packaged systems such as packaging machines, clean water generators and so on

So that more advanced technologies could be used to replace record keeping functions that were traditionally carried out on paper, the industry pressed the FDA for many years to get them to produce rules and guidelines on the use of electronic records and electronic signatures The FDA set up a task force and issued notice of its intent to issue a new rule The regulators needed to look at the key areas of regulatory acceptance, enforcement integrity, security, validation, existing industry standards for digital signing and freedom of information before making rules

Comments and information for building rules were solicited from industry After a period of collaboration with industry, the final 21 CFR Part 11 rule was published in March 1997 Most of the blame for the problems later to be discovered by the rule was generally laid at the doorstep of the FDA However it would seem that industry had sufficient time to work with the regulator to produce a more refined rule The FDA does say in the 1992 Federal Register entry that the issues to be faced with electronic records and signatures are complex and often beyond the scope of GMP This early reluctance to fully clarify scope was obvious throughout early guidance from the industry as to the implementation of the rule and led to problems later on with interpretation

The FDA, when considering making their ruling had targeted direct impact systems This did not mean that other systems with much smaller scope and with less potential product quality impact escaped from the requirements of the rule in the eyes of cautious manufacturers In fact, there seems to have been very few systems that fell outside the scope due to regulatory conservatism in the rule's interpretation

Farrell and Cooper [63] put the causes of the gap between perceived and actual intent of the rule down to three main factors, confusion between records required for predicate rule and other records, the imprecise terminology in use in the computing industry (i e anything on a computer can be termed to be a record), and the desire in the pharmaceutical industry to have definite direction and guidance for all its regulatory requirements They do not consider that a main cause of the gap might be

the reluctance of manufacturer's to employ risk based assessments of applicability, or the role suppliers might have played in 'pushing' a Part 11 agenda for competitive purposes

The objectives of Part 11 were to enhance production efficiency whilst maintaining predicate rule requirements for records and ensuring the integrity and security of those records [64] Although it was effective in 1997, the rule was not enforced until 1999 to allow the industry to get over its 'year 2000' [65] issues

The requirement placed constraints on the use of electronic rules and signatures Although their use was optional, manual methods had to be used where compliance with Part 11 was not demonstrable Woodrum [66] highlights interpretation issues with the rule One of her points is that although the rule was not meant to interfere with systems producing paper records in the traditional style, systems which use electronic records to produce the paper ones must be compliant with the rule The regulators guidelines in 1997 did not preclude legacy (already in use) systems from their scope

The interpretive issues with the rule led to what was somewhat of a backlash from the industry This provoked the FDA into withdrawing their guidance, replacing it with new guidance which had a narrower scope, allowed the use of risk assessments when determining the applicability of systems and stated that the FDA would exercise enforcement discretion on certain features of the rule [63][65][67][68]

However some reservations still remain about interpretation and abuse of the discretionary elements of the revised guidance [65][67]

Although the rule has requirements that are quite specific, they are not technologically new and industry standards for software development exist that contain many of the requirements of Part 11 [69] Nevertheless, the impact of the rule has been dramatic

2 1 2 European rules for drug manufacture

Directive 2001/83/EC [70] from the European Union says that pharmaceutical manufacturers must have suitable and sufficient technical equipment GMP equipment must be designed to suit their intended applications Where electronic systems are used in lieu of paper systems, the manufacturer must have validated systems proving that the data will be stored appropriately Electronic data should be protected appropriately against loss or damage

Validation studies should be used to enforce GMPs according to European rules That is, the testing should verify that the equipment is suitable for its intended purpose Any changes that affect the manufacturing process should be validated The European guidance requires that critical process should be validated Again, criticality is often subjective and must be determined by the manufacturer

As with the FDA rules, the European Commission requires that computer systems used in controlling or monitoring drug manufacturing processes should be validated Annex 11 of the European rules states that

"Where a computerised system replaces a manual operation, there should be no resultant decrease in product quality or quality assurance" [37]

There should be appropriate expertise available for the design and validation of systems Annex 11 of the EC rules also requires a life cycle approach for computer systems [37] The life cycle should include planning, specification, programming, testing, commissioning, documentation, operation, modifying and monitoring Many of these phases involve external developers

Software should be produced in accordance with a quality assurance system, should be thoroughly tested, and should include internal checks of correct entries and data processing Consideration should be given to building audit trails into software to capture all changes to data and use of the system For auditing purposes it should be possible to obtain print outs of the electronically stored data

Annex 11 requires that when outside agencies are used to provide computer services, then the responsibilities of the outside agencies should be clearly defined The developer falls into this category

Annex 15 of the EC rules says that the compliance of the design of systems with GMP should be demonstrated and documented and that they should be validated [70] The requirements from the European regulators for computerised systems are relatively sparse and less prescribed than those put forward by the FDA

2 1 2 Good Automated Manufacturing Practice (GAMP)

Trill [71] points out that much of the guidance for support of new technology is taken from industry bodies such as the ISPE, GAMP forum, PDA, Pharmaceutical Quality Group (PQG), and the ISO This guidance is usually well received by the regulators to the point that they are often quoted in regulatory literature and may eventually evolve as annexes to current regulations

Trill [71] speaks in particular of the evolution of GAMP into an industry standard He claims that a desire for better understanding of computerized solutions by the industry, together with a requirement for best practice and regulatory compliance in the late eighties resulted in its conception Negative inspection findings within the industry with regard to computerized systems were also a driving force for GAMP [13]

The Good Automated Manufacturing Practice (GAMP) forum is a sub-committee of the International Society of Pharmaceutical Engineering (ISPE) and the GAMP initiative has been endorsed by the FDA and the EMEA Its purpose is to aid *inter-*

alia pharmaceutical manufacturers in providing validated and GMP compliant automated systems The GAMP guide [13] is directed both at suppliers engaged in systems development and manufacturers for assessing those systems At the time of writing, the latest version of the guide is GAMP 4 It has *de facto* standard status in the industry

An outcome of the GAMP Forum project was the realization that in order to ensure quality of both software and ultimately the product, quality would be required to be demonstrably built in to the system code Suppliers were hence encouraged and pressurized into attaining greater regulatory compliance understanding when developing their systems In 2002, suppliers, developers and vendors were 'positively enthused' at this prospect of 'building quality into systems' [71]

The GAMP guide speaks of automated systems as being

'A broad range of systems, including automated manufacturing equipment, control systems, automated laboratory systems, manufacturing execution systems and computers running laboratory or manufacturing database systems The automated system consists of the hardware and software components, together with the controlled functions and associated documentation Automated systems are sometimes referred to as computerized systems, in this Guide the two terms are synonymous' [13]

This assertion is used in this research That is, automated and computerized systems shall be deemed equivalent

Automated systems can affect product quality either directly, or indirectly Quality must be built into the software to a sufficient degree to support the regulations The Medicines Controls Agency in the UK had discovered in their inspections in Europe and the US that there was a deficiency in understanding of technology and terminology related to software quality and validation [72] They observed that many companies were engaging in retrospective validation of a completed automated system based on the overall functionality rather than testing to verify the structural integrity of systems and their building blocks This was found to be a more expensive approach and did not meet with regulatory expectations

A 1988 report [73] to the UK government indicated that, in general, software was traditionally of poor quality, and required retrospective modification Another report to the same government department [74] recommended software quality standards be harmonised through ISO 9000

GMPs are targeted at the drug manufacturers rather than suppliers of equipment into that industry The GAMP guidelines serve to provide an accepted interpretation of the European and US GMPs and it provides specific guidance for suppliers

The development of guidelines by bodies such as the ISPE has been driven in part by the increased regulatory interest in computerised systems during inspections [75] The development of GAMP involved collaboration between suppliers and the pharmaceutical industry Its aim was to produce a standardised interpretation of the regulations

Automated systems consist of hardware, software and networked components A benefit quoted in the GAMP guide is that it offers a convergence of existing industry standards including ISO and IEEE standards and has relevance to both software and hardware

The fundamental framework behind GAMP is the 'V-model' This is a life-cycle compliant model that maps testing onto the specifications The model maps validation onto development to provide assurance that systems meet their design intent and to ensure that all aspects of design are tested The life-cycle model suggested by GAMP addresses the quality requirements of an automated entity, from conception to retirement The responsibilities in the 'V-model' section of the life cycle are split between the manufacturer and the developer, with ultimate responsibility lying with the manufacturer The 'V-model' is depicted in figure 2 1 2 1

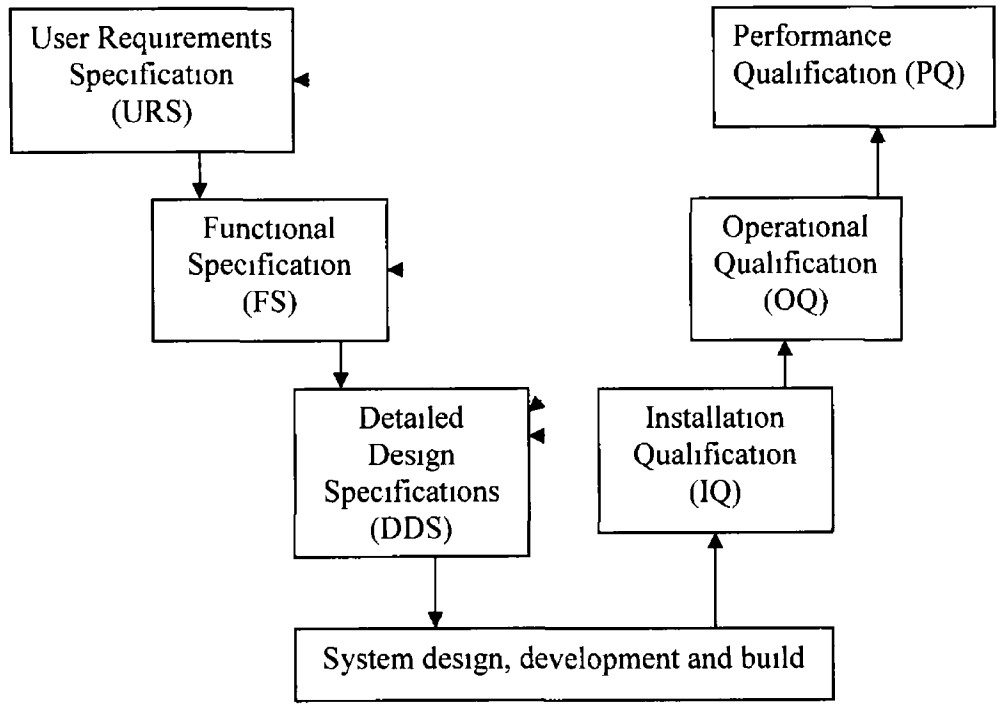


Figure 2 1 2 1 The GAMP 4 'V-model' for automated systems development for the Pharmaceutical industry

In figure 2 1 2 1, the solid arrows represent the sequential order of events and actions The dashed arrows represent verification relationships That is, PQ verifies the URS, OQ verifies the FS and DS and the IQ verifies the DS Each step deserves separate explanation, as their importance for pharmaceutical systems in pharmaceutical manufacturing environment is huge System developers whose products are used in pharmaceutical manufacture are expected to know and understand all the features of the GAMP model, even if they do not use or know the GAMP guide itself

The following is a summary of the important features of the GAMP V-Model

1 User Requirements Specification

The User Requirement Specification (URS) is the user's detailed specification of what the system should do It is a statement of the objectives and deliverables required for the automated system The URS tells suppliers what the user wants

2 Functional Specification

The Functional Specification (FS) is prepared by the supplier and tells the user how they can meet the user's needs It details the functionality they can offer to meet the user requirements

3 Detailed Design Specifications

The Detailed Design Specifications (DDS) are the supplier's detailed specifications for building the system DS includes hardware and software specifications necessary to ensure that a reliable system will be produced that will meet the user requirements

4 System design, development and build

This involves the design, design review, hardware and software building, software review and supplier testing of the automated system

5 Installation Qualification

The Installation Qualification (IQ) verifies that the supplied installation is as required on the target system and that basic functionality operates It involves inspection of drawings, design documents, instrument calibration certification and software version recording and verification The IQ documentation may be prepared by the vendor / developer of the system or can be produced by the manufacturer The same is true for the OQ

6 Operational Qualification

The Operational Qualification (OQ) tests the functionality of the system It verifies the FS It verifies normal and realistically abnormal operational conditions to ensure that the system can handle those conditions

7 Performance Qualification

In Performance Qualification (PQ) the system is operated in its intended operational environment The testing is mapped to the URS The system must do what it was

intended to do at the outset of the project and within pre-determined specification limits

The combined IQ, OQ and PQ constitute the system qualification or validation The system is released for operational use on successful completion of the PQ Validation however may continue into full system operation to ensure that the global process performs as intended during drug manufacture The developer can be involved in each of the phases on the 'V-model' from carrying out the associated tasks completely within a phase to providing supporting design and testing documentation to the manufacturer

Although the vendor - supplier relationship is still important in the operational phase or while the system is in its 'validated state' for the purposes of technical service and system modifications, it is in the V-model phases of the life cycle that the vendor's involvement is greatest

Treatment is given by the GAMP guide to categories of automated systems such as information systems, embedded control systems, process control and stand-alone systems The fundamentals of the life cycle and V-model apply whatever the automated entity

The contents of a user quality plan are suggested by GAMP and reinforce the supplier's responsibilities The suggested contents of a user quality plan are

1 Specification management
2 Design reviews
3 Programming standards and code reviews
4 Testing
5 Installation
6 Data migration
7 Factory and user site acceptance testing
8 Document management
9 Change control
10 Configuration management
11 Non-conformance and risk management
12 Project training
13 Handover to support organisations

ISO 9000-3 [76] and the TickIT [43] guide for software quality were used in the creation of GAMP [13] It was hence influenced by contemporary industry standards for software

Many things are taken into consideration when a manufacturer is selecting a vendor Among these are the vendor's quality commitments and approvals, their financial

stability (likelihood of survival), and ability to support end users [77] Biographies, references, and audits are tools that can be used to assess suitability GAMP 4 gives guidelines for conducting vendor audits and for audit preparation by vendors In addition to this, stringent controls are expected for software developers In accordance with GAMP and good software engineering expectations, criteria that may be used to establish best practice by developers include assessments of tools used by the developer, their general level of experience, and references from other pharmaceutical users of the software, change management system, and source code availability to the end user

2 2 Quality Systems

2 2 1 Quality Management and its effects

The influences that quality has on business performance are well documented in the literature The relationship between GMP and quality however is not so well covered Much work exists in the literature looking at the contribution to quality management by 'gurus' of quality such as Crosby, Deming, Juran and Feigenbaum (see [28],[30] and [31] for example) This work was not repeated here Of those gurus, the work of Philip Crosby was deemed most pertinent to this work because of his focus on Quality Management rather than techniques and because of his influence on software development systems such as the CMM

Sharp states that GMP is required for product quality, and ultimately for patient safety [5] He says that in a draft of the orange guide (early British guidance on GMP) that 'any so called GMP measure which does not contribute directly or indirectly to those ends is an irrelevance' The problem lies with defining what is meant by direct or indirect This has usually led to all activities being considered to at least having an indirect effect on GMP He puts the increased requirements for quality assurance in the manufacture of medicines down to the potential hazards that could accrue in environments where there is less than one hundred percent testing of all final drug products, which is not a practical possibility in most cases, as testing would be detrimental to the product Three important factors are identified by Sharp [5] justifying the heightened assurance requirements

1 Limitations on the testing of end products
2 The hazard that would result from even a small number of product defects
3 The low probability of detection (before consumption) of any defects by the drug recipient

Thus, the additional levels of quality assurance are passed onto system suppliers for the same reasons

The suggestion that quality is free and that there can never be too much quality in an organisation is much espoused by the quality guru Philip Crosby [78] He argues that quality has the ability to make a firm first among equals in a competitive environment

and that it is often the difference between success and failure Crosby identifies four fundamental 'pillars of quality' that lead to total quality success

These are

1 Management participation and attitude towards quality

2 Professional quality management within the organisation

3 Original quality programs

4 Recognition, both of internal quality and by external sources

Another recognized quality guru, Deming [79] claimed that quality reduces costs and increases market share In fact the rise of the quality professional has been attributed to increases in global competition, loss of market share, national quality award scheme and the ISO 9000 series of standards

Although quality can help to expand market share, cut costs, improve productivity and increase profits, quality alone will not suffice, activities such as marketing, product and process design and engineering amongst other factors, including the market itself all play roles [80] Positive relationships between quality, market share, and profitability are evident from the literature [28][30][31][80] consistent with the theories put forward by the quality gurus [78][79][81] The general finding from the literature across many sectors was of a weak to moderate positive relationship between quality practices and business performance Some work [80][82][83] used technical measures relating to the manufacturing process, whereas others used quality management measures to ascertain quality practice scores [28][30][84]-[86]

Customer focus, according to Dale [87], is the greatest motivator for quality improvement, followed by the need to keep costs down Competition can drive quality improvement programmes directly

Quality assurance, as distinct from quality control, should have features designed to *prevent* quality failures, rather than just consist of a series of checks to verify that no failures have occurred Three factors that can influence developers not to incorporate a distinct quality management structure into their *modus operandi* are perceptions that there is no added value from quality, that they 'do it anyway', and that it is a luxury rather than a requirement [88] These are naive and erroneous positions though as quality management is basically just a formal system of doing things right, or to use TQM vocabulary, doing the right things right

Quality should be embedded into every business process and there should be a balance between technical skills and quality skills for those who are involved with QA [89] Research indicates that organisations committed to quality management are more likely to have top management support, good communication on quality matters, and a high emphasis on customer service, yielding better business performance [30]

Although there are indications in the literature that formal structures such as TQM, ISO, and the SEI CMM can result in better quality and business performances,

informal structures, which rely on the same principles espoused by formal systems, can yield good results also TQM encapsulates a series of approaches, which involve customer focus, top-down quality leadership, statistical thinking, continuous improvement and teamwork [30][79]

Hamid [90] concluded in his research based on a NASA software project that there was an optimal QA input to a development project of around 15% of the total man hours spent on the project, and that the law of diminishing returns is invoked beyond this, meaning that the cost of the project increases with less returns on error detection during development The example analysed was very specific though, and differing interpretations of what is meant by quality would yield differing results In a TQM environment for instance, many more functions than fault detection, design reviews and walkthroughs comprise quality assurance Applying a rule of thumb for an optimal level of quality would contribute to losing sight of why quality is important at all, to make sure that everything is done the way it should be

Software quality assurance in general requires the same conditions to prevail as for general quality assurance in order for it to be successful For example as with ISO and TQM, top management have an important role in making software quality assurance successful Organisational structure is more important to successful quality performance than the selection and use of piecemeal quality practices [91]

A firm's performance at any point may be related to their progress on the quality journey In this work it was possible to determine progress based on a quality score derived from the established core quality practice criteria

Fundamental to any system is a set of key criteria, the achievement of which can ultimately improve quality and business performance A set of criteria derived from the literature is presented later in this work This was for two purposes Firstly it established that any organisation surveyed that claimed to have a formal quality system in operation had the fundamental criteria firmly established Secondly it allowed assessment of organisations without formal structures

In order to determine the overall picture of quality in an organisation, it was necessary to determine quality effectiveness as well as practices [92] Through the survey, data pertaining to quality effectiveness were obtained through the quality practice criteria

2 2 2 ISO quality systems

ISO 9001 2000 [93] lays out the general requirements for quality management systems for any organisation compliant with that standard ISO 9000-3 2004 [76] then maps those requirements onto a computer-engineering organisation It advocates the use of a life-cycle model for the production of software where testing is directly mapped onto requirements and quality begins at project conception and

ends at system retirement The central quality requirements for the general case and the software case are hence identical and can be seen summarised in table 2 2 2 1

Table 2 2 2 1 ISO 9000 2001and ISO 9000-3 2004 requirements for quality systems

ISO 9000 2001 and ISO 9000-3 2004 requirements for quality systems	
1	Process approach
2	Documentation and record management
3	Quality manual
4	Management commitment and policy
5	Customer focus
6	Quality policy
7	Planning
8	Assigned responsibility
9	Communication
10	Management review
11	Resource management
12	Human resource management
13	Training
14	Infrastructure
15	Product realisation (customer interaction and planning)
16	Requirements review
17	Design and development planning, review and validation
18	Design change control
19	Purchasing management
20	Service provision
21	Measurement, analysis and improvement
22	Audits
23	Non-conformance resolution

ISO 9000 influences better quality performance [94] and can provide a useful first step or framework for a developing TQM organisation [28] [95] [96]

ISO 9000 is customer and performance focused but applies to the quality management system, not the product or service offered by the firm Advantages of being accredited to such a standard include companies having more precise specifications, ultimately a better quality product, effective systems for dealing with

customer feedback, general increases in workmanship and an improved reputation ISO 9000 companies tend to notice increased sales [92]

The ISO series of standards are limited however Braa and Ogrim [97] criticise them on the basis that they are too static By virtue of the standard requiring fixed specifications, being completely documentation driven, and not involving the end-users enough in the software development they do not necessarily ensure high quality This can lead to low quality performance if a company's internal requirements are of low quality That is, the standard provides a framework to organisations to prove that they can meet their own internal requirements, regardless of the requirements However, there is nothing in the ISO standard that means that software specifications cannot be revised as the need arises, as long as the revisions are controlled Hence the interpretation of the standard by Braa and Ogrim with regards to fixed specifications may be seen as rigid

The problem with fixed requirements is that they can prohibit the advantages brought about by cyclical or incremental development and basing all decisions on pre-determined documentation can lead to compliance to something that is not always in the best interest of the end user Braa and Ogrim [97] recommend a circumspective application of the ISO standards They also warn of 'symbolic' or valueless application in order to improve competitiveness through aesthetic certification

Andrews says that ISO9000 / 9001 are not targeted to software design [35] and validation and that whereas ISO9000-3 does go some way, it does not go far enough to meet GMP requirements However, as ISO offers a quality management framework, it is up the supplier to ensure that the elements of the ISO standards are effective for their processes, the ISO standards can be applicable to a software environment with careful application

2 2 3 Total Quality Management

TQM is defined by the ISO8402 standard as

"A management philosophy embracing all activities through which the needs and expectations of the customer and the community, and the objectives of the organisation are satisfied in the most efficient and cost effective way by maximising the potential of all employees in a continuing drive for improvement" [98]

TQM is claimed by Dale [87] to have been a major contributing factor in the rise of the Japanese manufacturing sector The basic premise of TQM is that all members of an organisation are actively involved in the quality structure and the improvement processes The key elements of TQM as defined by Kan and Basili [99] are

1 Focus on customer satisfaction
2 Process improvement (both product and business processes)

3 Company wide quality culture

4 Measurement and analysis

TQM gurus are united in their view that customer focus is a primary feature of TQM [99] Total Quality Management (TQM) involves complete interaction between all internal and external customers, suppliers, stakeholders and greater society for a given organisation [92] It requires effective and efficient management of all processes TQM involves long-term quality improvements and commitments

The BS7850 TQM standard [100] says that every person in an organisation must be used to his or her fullest potential if the goal of total quality is to be achieved Customer satisfaction, investment in people and training are three major features of the standard It defines a process in an organisation as being any activity that accepts inputs, adds value to these inputs for customers, and produces outputs for these customers TQM involves maximising efficiency and effectiveness for all processes that an organisation engages in It gives examples of quality losses and mentions *inter alia* loss of customer satisfaction and loss of opportunity to add more value to the customer, the organisation and society as being losses This is an indicator of the totality of the approach Functions within a company that would normally be away from the production coalface such as administration, accounts, IT departments and so on should be fully included in quality management and improvement processes

Chou et al [101] equate the plan – do –check – act phases associated with TQM to the quality elements of a software life cycle stages as follows 'Planning' is when the requirements are being analysed, 'doing' is the system development, 'checking' is the testing or validation phase and 'acting' is the implementation and maintenance phase of the life-cycle

According to Chou et al [101] the key elements of TQM include customer focus, obsession with quality, scientific approach to quality, long term commitment, teamwork, continuous improvement, education and training, freedom to change through control, unity of purpose, and employee involvement and empowerment

Ismail and Hashmi [28] said that about three-quarters of TQM implementations are in companies with less than 250 staff (based on an Irish survey) However performance is only enhanced through TQM for manufacturers who have more than 50 employees A marginal increase in performance was observed from their survey analysis for ISO registered firms adopting TQM Substantial performance differences did exist in Ismail and Hashmi [28] between the performances of these firms and firms without TQM or ISO

The permanency of TQM in an organisation is related to the level of TQM adoption Dale [87] identifies six levels of adoption or practice of TQM

1 Uncommitted to TQM (no formal TQM process)

2 Drifters (Short-term view TQM aware, but not convinced of its value)

3 Tool-Pushers (Lots of quality tools such as Statistical Process Control Award focused Tools not appropriately used or linked to a 'total' strategy Pre-occupied with numbers)

4 Improvers (Good quality infrastructure although doesn't pervade the entire organisation)

5 Award Winners (Can compete for top quality awards, Quality is 'total')

6 World class (Total quality works to 'delight' the customer Never-ending pursuit of improvement and complete customer satisfaction)

Dale [87] says that permanency of TQM is strong only for improvers, award winners and world-class practitioners

Quantitative assessment is fundamental to ensuring TQM [102] and cost of quality is a central measurement feature Quality costs typically range from 5% to 25% of sales turnovers in manufacturing organisations, Cost effective quality management systems can reduce cost of quality by two thirds [87] according to Dale However this is a theoretical assertion and generalizations may be invalid

Cost of Quality (COQ) measurements are important as they help to focus organisational improvement and categorise that improvement Through careful definition of measures within an organization including cost of failure, COQ can be ascertained

Morse [103] says that cost of quality can have four uses

1 To promote product and service quality
2 To give rise to performance measures
3 Provides means for budgeting for and controlling COQ
4 Motivators

It is also a performance indicator that can be used in vendor approval

Cost of Quality (COQ) measurement is useful to determine actual costs and to drive improvement measures at management levels Costs include costs of both conformance and non-conformance, and TQM should aim to minimise both Cost of conformance as defined by BS6143-1 1992 is

"The intrinsic cost of providing products or services to declared standards by a given, specified process in a fully effective manner" [104]

In the same standard, cost of non-conformance is

"The cost of wasted time, materials and capacity (resources) associated with a process in the receipt, production, despatch and correction of unsatisfactory goods and services" [104]

Process cost elements should include people, equipment, materials and the relevant environment Costs can be further subdivided into prevention costs, appraisal costs, internal failure costs such as waste and poor productivity, and external costs such as loss in sales and growth [104] Increased quality awareness and improvement serves to reduce all such costs The total cost of quality can typically be expressed as a percentage of sales revenue for reporting purposes

Krishnan [105] established that costs of development and support for software products increased in line with quality He challenges the application of Crosby's much-cited hypothesis that quality is free to the area of software development [78] Crosby's philosophy is taken out of context Crosby says that by adding quality, which does have a finite cost, defects can be lowered and profits increased, thus paying for quality In order to realistically challenge this, an empirical assessment would be required that compared pay-offs against absolute quality costs Krishnan [105] ultimately asserts in conclusion that Crosby [78] is upheld in that by excluding other factors, higher quality reduces costs The effects that increased quality inputs have on profit or business performance are not ascertained in the study, which are fundamental to Crosby's theories The sampling frame in this study was restricted to 27 projects from the same software development company This may be seen as a significantly biased study in the sense that it may not be feasible to generalise based on the practices of a single firm's quality management practices

Krishnan's study [105] indicated that for more complex software projects, cost decreases with quality inputs by a greater amount than for less complex software.

The use of tools in a quality environment does not ensure success, as effectiveness is not guaranteed. However their use can be an indication of a mature quality system. Dale [87] lists a series of tools and techniques that are best known in TQM as shown in Table 2.2.3.1.

Table 2.2.3.1: Series of tools and techniques that are best known in TQM according to Dale [87].

Tool	Main features
Checklists	Prompts for checking key features of processes, equipment, systems, products or services.
Flow charts	Process maps for operations, systems and functions.
Histograms	Graphical representation of event occurrence based on frequency of occurrence.
Graphs	Used to convey key data.
Pareto diagrams	Statistical diagram used to prioritise factors in a given global measure.
Cause and effect diagrams	Used to determine main causes of a given event.
Scatter diagrams	Used to plot data for the purposes of determining relationships between variables.
Control charts	Used to collect data about a given process and determine whether it is operating inside pre-determined limits.
Quality costing	Ascertaining the cost of quality
Statistical Process control	Control of the process through use of statistics.
Failure mode and effects analysis	A risk assessment method for improving design of products and processes by analysing all likely failures and mitigating against their occurrence.
Fault tree analysis	Analysis of possible causes of a fault starting at the system level and working down through each sub-system, equipment, materials etc. looking at all possible causes.
Design of experiments	Mathematical techniques used to define process parameters.
Quality function deployment	A system for mapping customer requirements into organisational structure and processes.

Tool	Main features
Affinity diagrams	Used to collect verbal data in complex situations and link statements together to produce order and analysis
Relations diagrams	Used to identify, understand and clarify complex cause and effect relationships
Systematic (tree) diagrams	Evolving diagram used to produce a hierarchy of tasks to solve a given problem
Matrix diagrams	Table used to assess the relationship between results and causes or between objectives and methods
Matrix data analysis	Used to order and analyse matrix diagrams
Process decision chart and arrow diagrams	Used to select the best process from a choice of processes to solve a given problem
Departmental purpose analysis	Assessment technique for improving departmental purpose
Mistake proofing	Uses detailed analysis of the source of defects to prevent their recurrence
Benchmarking	Benchmarking practices and performance against competitors or best in class organisations for the purposes of improvement

2 2 4 Software Quality

Software defects are common and tolerated with most applications, but should be eliminated for critical applications Rodford [106] claims that design inspection, code inspection, quality assurance and testing used throughout the development life cycle can produce median defect removal rates of 99% from software

Concerns about software quality are well documented [107] - [109] Unfortunately there has been acceptance by the wider software market of the trade off between low quality and better features speedily delivered [108] As software processes mature, there are increasing numbers of companies focusing on both reliable quality and enhanced functionality Today, as in the past, QA knowledge by software

developers spans a large range, from those who are barely familiar to those totally adept or willing to become so [110]

There is genuine reason for manufacturers and regulators to be concerned about software quality Hayes [109] reported from a survey of user businesses on software quality that only 45% of those questioned reported satisfaction about the commercial software they had purchased 76% of the respondents said that quality was a significant consideration when choosing a software vendor

Evidence exists of some vendors pricing their software products based on key quality factors [111] That is, price is linked to customer satisfaction giving a very visible reflection to the customer of the vendor's quality performance and a huge incentive for vendors to maximise total quality

Quality management and software quality monitoring should be given rigorous treatment and should be approached scientifically [112] There are many features that must be planned into software design, which cannot be retrospectively integrated successfully For example, building security into critical software is a fundamental design requirement Software should be built around a security frame and it should not be added on as an afterthought [113] Quality planning can ensure such requirements are managed

In any software project, documentation management makes up a vital element in ensuring that the actual product matches the intended product [114] This is extremely important in software quality assurance due to the difficulties with assessing the finished product, owing to the hidden nature of the code Research indicates that there has been significant dissatisfaction with software quality by users, particularly for bespoke software Poor documentation has often been cited as been a source of user dissatisfaction [115]

Software Quality Assurance (SQA) began in the 1960s with IBM's final product testing [116] SQA can often occur too late in the software cycle to add real value Software quality for regulated industries in general means adhering to requirements approved by the regulators, amongst the litany of requirements laid down by non industry-specific standards

There is evidence in the literature that increasing investment in SQA is required amongst system developers Of 100 Malaysian companies surveyed by Ow and Yaacob [117], most reported low investments in SQA and also acknowledged the need for higher investment Commercial companies reported the highest investments on average In general it is not wise for developers solely to review and inspect their own systems as this can lead to lower than desired product quality That is, the development company should employ independent quality assurance personnel to verify design work, to supplement the development engineering team's own reviews

Ow and Yaacob [117] recognise ISO and CMM as being two of the most important quality frameworks relevant to software development in Malaysia

The primary goals of SQA are to monitor the software development, ensure compliance with standards and procedures, and to highlight improvement requirements to management It should do this through independent observations Runeson [118] suggests an appropriate SQA organizational structure consisting of a separate SQA function with auditing relationships with the project staff and project manager, and a reporting function to the senior manager

SQA includes the technical methods and tools that aid in the design and construction of high quality software ISO 9000, the SEI CMM and TQM can be used as methods to achieve SQA [101] CMM involves an SQA function However, SQA within CMM is not solely responsible for quality, this lies with all the elements of the development project team SQA involves reviews of project literature, audits to check adherence and measurements to determine compliance to processes and to ascertain progress information SQA essentially monitors the controls developed by quality management, both functions being fundamental to the quality effort required by CMM

The selection of an appropriate software quality assurance programme is a vital project management step in software development [119] Software produced under

an accredited quality assurance scheme can improve buyer confidence, especially when the developer is accredited by national bodies [115]

Standards are tools for showing compliance with regulations, policies and guidance according to Herrmann [120] When there are overlapping or conflicting standards there can be difficulty following and implementing standards No single standard can be followed which can yield the desired quality of a software product for use in a regulated activity, rather a series of appropriate standards should be used for the purpose [121]

Other models exist for software quality such as the 'TickIT' initiative [43] but are not advocated widely in the literature [121] with regards to achieving regulatory compliance

Many models such as GAMP are built on industry standards such as the ISO standards already described and standards developed by the IEEE For example, the IEEE standard 730-1998 [122] provides the requirements for quality assurance plans for critical software Critical software in this case is said to be *inter-alia* any where failure can have safety implications The standard contains many features familiar to other standards and guides such as GAMP, the ISO9000 series and the CMM [14] Its scope equates firmware to software The minimum requirements for a SQA plan are presented in order to give developers a baseline against which to

assess their own SQA plan against Table 2 2 4 1 shows the key features of IEEE 730-1998 [122] for software quality assurance plans

Table 2 2 4 1 Key features of software quality assurance plans for critical software according to ISO 730-1998 [122]

Required sections	Key Features of plan section
Purpose	Specifics on scope of plan including software details
Reference Documents	All documents referenced in plan
Management	Description of the organisational structure and how it affects quality, responsibilities, reference to the software life cycle phase developed under the plan, tasks to be carried out under the plan, sequence of tasks in the project with emphasis on quality related tasks
Documentation	Identify all design, verification, and operation and maintenance documentation Design documentation should include requirements specifications, design description Verification documentation should include a validation plan and report There should be a plan to deal with configuration management for configurable software
Standards, practices, conventions and metrics	Identification of standards and practices to be used and how compliance to them will be handled Detailed design standards for logic structure, coding, testing and metrics
Reviews and audits	Definition and logistics of technical and management audit requirements At a minimum these must include software requirements reviews, preliminary design reviews (management overview), critical design reviews (or detailed design review), verification and validation plan review, functional audit before software delivery to ensure all software requirements have been met, physical audit of pre-delivery software and documentation, in-process audits to ensure continuous adherence to standards and requirements during design, managerial reviews of the SQA plan, configuration management plan review, and post-project post-mortem reviews
Test	Test sections excluded from the verification and validation plan
Problem reporting and corrective action	Mechanisms for resolving problems and issues
Tools, techniques and methodologies	Identification of special tools and techniques used to implement the SQA plan
Code control	Methods for software code storage and control
Media control	Physical media requirements for the software product
Supplier control	Requirements for supplier's software Suppliers must also have an SQA plan

Required sections	Key Features of plan section
Records collection, maintenance and retention	SQA documents to be retained including their retention duration
Training	Training requirements to meet the SQA plan
Risk management	Methodology used to assess risk during the life-cycle phase

The IEEE/EIA 12207 0 [42] standard, which is also ISO/IEC 12207 1995, is a standard for software life cycle processes for Information Technology and was influenced by IEEE 1074 [41] It applies to the software portion of firmware as much as to computer based software It provides a framework for lifecycles, but does not give details as to implementation techniques The life cycles used by developers must be mapped onto the IEEE 12207 0 standards requirements in order to prove compliance It divides the life cycle process into 3 blocks, Primary life cycle processes, supporting life cycle processes and organisational life cycle processes as follows

1 Primary Life cycle processes consisting of acquisition, supply, operation, development and maintenance
2 Supporting Life cycle processes consisting of documentation, configuration management, quality assurance, verification, validation, joint review, audits and problem resolution
3 Organisational life cycle processes consisting of management, infrastructure, improvement and training

The development process consists of thirteen activities Table 2 2 4 2 outlines those activities and details their primary features Documentation of all activities is required by the standard

Table 2 2 4 2 Development activities and primary features of the IEEE/EIA 12207 0 standard [42]

Development Activity	Primary features
Process implementation	Define a lifecycle to be used Document all project outputs Place outputs under configuration management Document and resolve problems and non-conformances Choose and document standards and programming languages Develop project plans that include all the requirements of the standard
System requirements analysis	Document the specific intended use of the system Define functions, capabilities, and all system requirements
System architectural design	Build a top-level architecture of the system identifying all configurable items
Software requirements analysis	Establish and document software requirements including quality characteristics
Software architectural design	Transform requirements into an architecture Develop preliminary user documentation, top-level design and test requirements
Software detailed design	Develop design into smaller units that can be coded
Software coding and testing	Develop each software unit Develop test plans and carry out testing
Software integration	Develop a plan to integrate coded units Integrate and test unit integration
Software qualification testing	Evaluate and test the software
System integration	The software and hardware should be integrated and configuration managed The integration should be tested
System qualification testing	Testing should take place that maps the requirements to the completed system
Software installation	Install software according to a plan The installation should be verified against requirements and basic operation checked and documented
Software acceptance support	Support the end users acceptance review and testing of the product Provide continued training and support

2.2.4.1 The Capability Maturity Model

The Capability Maturity Model (CMM) from the Software Engineering Institute (SEI) of Carnegie Mellon University in Pennsylvania [14], USA, uses a 5 stage maturity framework to allow growth in capability with the objectives of improving software development processes and improving software quality. The model is centred on the principles of sustained continuous process improvement and sound quality practices. The model used derives many of its principles from the recognised quality gurus like Crosby, Deming and Juran. It defines a maturity level as

"A well-defined evolutionary plateau toward achieving a mature software process" [14]

The CMM [14] was developed in the USA with military sponsorship. It was intended for evaluating US Department of Defence software contractors but has been adopted by civilian software developers worldwide [123]. It consists of five levels of organisational software process maturity levels. CMM organisations must pass through each level.

Each level is focused on moving to the next level. The final level requires continuously improving beyond the requirements of that level. Although CMM does not tell how to get to the next level, it gives high-level guidance on where an organisation needs to be to have achieved it. There are a series of 'Key Process

Areas' or KPAs that must be established for any given level to be seen as complete

The maturity levels, and the KPAs associated with them are detailed in table 2 2 4 1 1

Table 2 2 4 1 1 The maturity levels and the Key Process Areas (KPAs) associated with the CMM

Maturity Level	Characteristics of maturity level	Key process areas
1 Initial	Ad hoc, chaotic processes Success based on individual effort	None
2 Repeatable	Basic project management processes for finance, schedule and functionality Can be repeated for instances of similar projects	Software configuration management Software quality assurance Software subcontract management Software project tracking and oversight Software project planning Requirements management
3 Defined	A single defined organisational software process approach in use that pervades management and engineering functions	Peer reviews Inter-group coordination Software product engineering Integrated software management Training program Organization process definition Organizational process focus
4 Managed	The defined process and product quality are measured, controlled and understood	Software quality management Quantitative process management
5 Optimizing	The process is continually approved through use of quantitative feedback and innovative techniques	Process change management Technology change management Defect prevention

The CMM identifies five common features of the key process areas These are

1 Commitment to perform including establishing policies and senior management sponsorship
2 Ability to perform, including training and organisational structure
3 Activities performed, including procedures and tracking
4 Measurement and analysis
5 Verifying implementation, typically through audits and software quality assurance initiatives

The CMM has become a *de-facto* standard for software processes and for assessing organisational capability maturity, it is probably in wider use in the US than the ISO 9000/9001 series of standards for quality and software development [118][124]

The SEI CMM can be used as a framework to support the process improvement aspects of TQM for software developers [99] TQM can be seen as the integration of project, process and quality management for software development Measurement and analysis is important as a means of quantifying current performance trends and making improvements in software quality

Because of the complexity of software and the invisible nature of the building blocks of the finished product, structure is required in software design and testing A quality system can fulfil this role and CMM can be used for this purpose

Software Quality Engineering (SQE) within the CMM involves quality development elements, which are prospective in order to achieve quality in the software product, as well as Quality Assurance (QA) to assure that the required quality is achieved Activities in development include tasks such as requirements engineering, system and software design and implementation of the software Activities in QA include SQA, general quality management and testing SQA is said to be all those activities that provide independent assurance that prescribed processes and procedures are adhered to These processes and procedures are defined through the quality management effort within a CMM environment

2 3 Comparisons between quality management systems and the development of primary practice criteria

Some of the review work for this thesis involved near exhaustive trawls of the literature on quality management in order to develop sets of criteria and measures reflective of effective quality practices This section extracts from and expands on that work but does not aim to repeat it This work aimed to limit the number of constructs required for the survey to a manageable, practical level Appendix D outlines all the literature reviewed and the corresponding criteria deemed important by the respective literature reference The main findings from the review of these criteria are discussed below in section 2 3 1 The criteria that were for further consideration in this work are summarised in section 2 3 2

2 3 1 Overview of collated quality practice criteria

Adam et al [31] used average percent items defective, cost of quality and customer satisfaction to measure quality performance Rao, Ragu and Solis [94] identified seven general factors that underlie quality practices

1 Leadership
2 Information and analysis
3 Strategic quality planning
4 Human resource development
5 Quality assurance system
6 Supplier relationships
7 Customer orientation

The European Quality Award (EQA) [16] from the European Foundation for Quality Management (EFQA) used two sets of criteria for establishing levels of organisational excellence These could be broken into 'enabler' criteria and 'results' criteria Specific parameters for performance measurement were not provided Applicants must submit information on how they assess the criteria within their organisations together with any results and targets Information about competitor's performances and 'best in class' performance was also required (where available) in the model The five 'Enabler' criteria and four 'Results' criteria were each given a 50% weighting of the total score Each main criterion was also given an even

weighting within their criteria type For example, 'Leadership' and 'Processes' each had a 10% weighting of the total score 'People results' and 'Society Results' each had a 12 5% weighting

The criteria used to assess EQA applicants together with their weighting, is produced in table 2 3 1 1 below

Table 2 3 1 1 The criteria used to assess EQA [16] applicants together with their weightings

Criteria Number	Type	Criteria / Sub Criteria Name	Weighting of sub-criteria (as a percentage of criteria)
1	Enabler	*Leadership*	
a		Leaders develop the mission, vision, value and ethics and are role models of an excellence culture	20%
b		Leaders are personally involved in ensuring the organisation's management system is developed, implemented and continuously improved	20%
c		Leaders interact with customers, partners and representatives of society	20%
d		Leaders reinforce a culture of excellence	20%
e		Leaders identify and champion change	20%
2	Enabler	*Policy and Strategy*	
a		Policy and strategy is based on the present and future needs and expectations of stakeholders	25%
b		Policy and strategy are based on information from performance measurement, research, learning and external related activities	25%
c		Policy and strategy are developed, reviewed and updated	25%
d		Policy and strategy are communicated and deployed through a framework of key processes	25%
3	Enabler	*People*	

Criteria Number	Type	Criteria / Sub Criteria Name	Weighting of sub-criteria (as a percentage of criteria)
a		People resources are planned, managed and improved	20%
b		People's knowledge and competencies are identified, developed and sustained	20%
c		People are involved and empowered	20%
d		People and the organisation have a dialogue	20%
e		People are rewarded, recognised and cared for	20%
4	Enabler	*Partnerships and Resources*	
a		External partnerships are managed	20%
b		Finances are managed	20%
c		Buildings, equipment and materials are managed	20%
d		Technology is managed	20%
e		Information and knowledge are managed	20%
5	Enabler	*Processes*	
a		Processes are systematically designed and managed	25%
b		Processes are improved, as needed, using innovation in order to fully satisfy and generate increasing value for customers and other stakeholders	25%
c		Products and services are designed and developed based on customer needs and expectation	25%
d		Products and services are produced, delivered and serviced	25%
6	Results	*Customer Results*	
a		Perception Measures	75%
b		Performance Indicators	25%
7	Results	*People Results*	
a		Perception Measures	75%
b		Performance Indicators	25%
8	Results	*Society Results*	
a		Perception Measures	25%
b		Performance Indicators	75%
9	Results	*Key Performance Results*	
a		Perception Measures	50%
b		Performance Indicators	50%

The Malcolm Baldrige National Quality Award (MBNQA) provided criteria for quality and business performance measurement used extensively in both the literature and in business [15] The American NIST (National Institute of Standards and Technology) sponsors the award scheme The criteria were developed and based on a set of defined core values and concepts These values and concepts were

1 Leadership

2 Customer driven excellence

3 Organisational and personal learning

4 Valuing employees and partners

5 Agility (capacity for rapid change and flexibility)

6 Focus on the future

7 Managing for innovation

8 Management by fact (using measurement and performance analysis)

9 Social responsibility

10 Focus on results and creating value, and a systems perspective

Seven criteria were detailed for performance measurement by the system They were scored according to the following table 2 3 1 2 based on a maximum score of 1000

Table 2 3 1 2 Criteria and scoring system for the MBNQA

Criteria	Score	Total
1 Leadership		*120*
1 1 Organisational Leadership	70	
1 2 Social responsibility	50	
2 Strategic planning		*85*
2 1 Strategy development	40	
2 2 Strategy deployment	45	
3 Customer and market focus		*85*
3 1 Customer and market knowledge	40	
3 2 Customer relationships and satisfaction	45	
4 Measurement, Analysis and knowledge management		*90*
4 1 Measurement and analysis of organisational performance	45	
4 2 Information and knowledge management	45	
5 Human resource focus		*85*
5 1 Work systems	35	
5 2 Employee learning and motivation	25	
5 3 Employee well-being and satisfaction	25	
6 Process Management		*85*
6 1 Value creation processes	50	
6 2 Support processes	35	
7 Business results		*450*
7 1 Customer focused results	75	
7 2 Product and service results	75	
7 3 Financial and market results	75	
7 4 Human resource results	75	
7 5 Organisational effectiveness results	75	
7 6 Governance and social responsibility results	75	

Aziz, Chan and Metcalfe [125] surveyed the use of a series of quality techniques when comparing quality practices in UK and Malaysian manufacturing These techniques were specific to each area of the production process and to employees of the company They are summarised in table 2 3 1 3

Table 2 3 1 3 Quality techniques used in UK and Malaysian manufacturing [125]

Operations	Quality Technique
Goods In	100% inspection
	Sample inspection
	No-inspection – rework at own expense
	No-inspection – rework at supplier's expense
	No inspection – supplier's QA reliable
	JIT
Manufacturing	100% inspection
	Sample inspection
	Control charts on process variables
	Control charts on results of 100% or sample inspection
	Process capability studies
	Failure mode and effects analysis
Goods out	100% inspection
	Sample inspection
	Product audits
Design	Market research
	Quality planning
	Failure mode and effects analysis
	Process capability studies
	Statistically designed experiments
	Taguchi experiments
Employees	Written quality policy
	Quality awareness campaigns
	Quality training programmes
	Customer surveys
	Quality costs
	Written work procedures
	Inter-departmental quality improvement teams
	Intra-departmental improvement teams
	Quality facilitators
	Employee suggestion schemes
	'Seven basic tools for QC'
	Deming cycle
	'Seven management tools for QC'
	ISO9000 registration

Crosby [78] defined the cost of quality as the expense of doing things wrong He developed a 5-stage maturity model for organisational quality management Level 1 is 'Uncertainty' meaning that quality is thought of at the low levels in a company, there is measurement of Cost of Quality (COQ) and that management are in denial of the need for better quality management Level 2 is 'Awakening' Here firms recognise that quality management can help and there is inspection and testing earlier in the process than for an 'Uncertainty' firm There is a reluctance to allocate resources, improvements are near sighted and the quality system is disorganised Level 3 is 'Enlightenment' Here a formal quality improvement structure exists, an organised quality unit, a no blame culture and cost of quality is measured in some way Level 4 is 'Wisdom' which encounters very few or no quality problems When they occur, they disappear quickly Accurate and realistic quality costs are obtained People wonder why the quality department exists Level 5 of Crosby's maturity scale is 'Certainty' In a Certainty firm the Quality Manager is considered vital and is on the board of directors There is dynamic and continuous restructuring of the quality improvement teams

Crosby [78] offers a self-administered tool for firms to establish their quality management maturity level The criteria therein was modified and included in this study when determining the quality maturity of firms being surveyed Several statements were made in Crosby's tool about quality practices that relate to each level of maturity The respondent then selects one statement that most closely

describes their practice A set of statements for each level of maturity is presented for seven categories

1 Management understanding and attitude
2 Quality organisational status
3 Problem handling
4 Cost of quality as a percentage of sales
5 Quality improvement actions
6 Summation of company quality posture

A problem with the tool is that the statements are made in a table where the heading is the level of maturity Hence, a respondent who sees their employer as having a 'Certainty' culture might mark the certainty column statements regardless of their accurate quality management posture It was necessary therefore when determining maturity levels from a survey to separate the statements so that the respondent does not know the implications of selecting a particular statement as being the closest description of their practices

In obtaining quality practice scores by survey, very few of the standard quality measures considered vital in other research were considered by Lee et al [82] although the MBNQA [15] criteria are referred to in their work Omissions include process improvement and management commitment

The paper by Ismail and Hashmi [28] identified six main elements, for use in a survey, as being critical to quality commitment determination These were management commitment, education and training, feedback measurement, total employee involvement, technological factors and continuous improvement The MBNQA [15] criteria were used heavily in the derivation of these criteria

From a trawl of the TQM literature by Yee Tsang and Antony [126], several factors were identified as being critical success factors for TQM The factors were classified as

1 Customer focus
2 Teamwork and employee involvement
3 Continuous improvement
4 Top management commitment and recognition
5 Training and development
6 Quality system and development
7 Supervisory leadership
8 Communication within the company
9 Supplier partnership and supplier management
10 Measurement and feedback
11 Cultural change

In their survey, Yee Tsang and Antony [126] found that 'Customer focus', 'Continuous improvement' and 'Top management commitment and recognition' were the most critical success factors in the UK service industry This is deemed to be consistent with the general consensus for manufacturing industries

If the TQM programme is not implemented correctly, then business performance may not be positively affected [127] Hackman and Wageman [127] listed seven change principles and five practices that should be in place for an organisation's quality management to be considered total

Hackman and Wageman's [127] Change principles

1 Focus on work in progress

2 Analyse variability

3 Manage by fact

4 Commitment to learning and continuous improvement

5 Knowledge of customer requirements as a test for evaluating change processes

6 Supplier partnerships to ensure that materials entering the organisation are of acceptable quality

7 Cross-functional teams for decision making on system wide problems

Hackman and Wageman's [127] Key practices indicative of total quality

1 Formation of short-term problem solving teams
2 Training
3 Top down implementation
4 Developed supplier relationships
5 Obtain data about customers

McAdam and Bannister [128] used these principles and practices as a measuring framework for business performance and change management within TQM Customer focus was again deemed to be a major factor in any quality practice measurement survey

The case study carried out into quality performance within a TQM company by McAdam and Bannister [128] used measures that were categorised under the headings of

1 Leadership and management commitment
2 Policy and strategy
3 Processes
4 Employee resource
5 Business results
6 Customer satisfaction

7 Teamwork

8 Employee motivation

Parzinger and Nath [129] identified eight TQM implementation factors that positively affected software quality based on survey data from software development houses and the literature

1 Employee empowerment

2 Quality measures and tools

3 Executive commitment

4 General Training

5 Customer needs assessment

6 Process evaluation

7 Quality training

8 Cycle time reduction

These eight criteria were compared against both the MBNQA [15] criteria, and also a selection of research works from the literature on TQM The comparison matrix in Parzinger and Nath [129] showed that all eight factors covered all the MBNQA criteria and the criteria derived from the five research papers considered Employee empowerment, customer needs assessment and specific skills training were deduced to be the three most important implementation factors In addition to TQM,

customer satisfaction was found to have positive association with the CMM maturity level attained by a firm [129]

In terms of the measurement criteria used in software environments, it has to be understood that there are broad similarities between CMM SQA criteria and ISO 9001[118] and a short analysis is necessary to deduce criteria Although they both require internal auditing of quality systems compliance, the methodology employed by each is different SQA reports audit results directly to the source of the findings as well as to management, whereas ISO 9001 generally involves reporting to quality management and up to senior management

The ISO 9000-3 [76] standard compares with the SEI CMM [14] model in that they both require defined and formalized software processes, standard objective evaluations by independent assessors and continuous internal audits with a view to product and process improvement [130] The ISO standard is not as detailed or formalised as the CMM standard, but it has a greater organisational reach, starting at top management The CMM standard is more relevant to sub-projects within a greater organisation

Ghosh [123] recognises that the CMM and the ISO 9000 series have much in common Ten major commonalities are summarised, and seven fundamental differences in his paper Also, four process elements are identified as unique to each system The commonalities and differences are identified in table 2 3 1 4

Table 2 3 1 4 Commonalities and differences between ISO 9000 software standards and the CMM based on Ghosh [123]

Commonality	Difference	Process elements unique to ISO 9000	Process elements unique to CMM
Both aim at consistent delivery of quality	CMM is specifically for software development ISO is for all industries	Contract management	Project tracking
Both include quality improvement of the product	ISO has a corporate focus CMM is software engineering focused only	Purchase and customer supplied components	Process and technology change management
Both require quality to be planned	ISO is more concerned with what to do than how to do it CMM has more 'how' information	Personnel issues (other than training)	Inter-group coordination to meet customer requirements
Both require high level commitment and formal quality statements	CMM is technically detailed ISO is not	Packaging, delivery and installation	Organisation wide process focus, process development and integrated management
Both emphasise prevention over correction of faults	ISO has a pass/fail certification structure CMM has levels of maturity		
Both require formally documented processes	CMM has a stepwise sequence for compliance ISO has no sequence		
Both require adherence and monitoring of processes	There are unique process elements exclusive to each system		
Both require that process outcomes be documented			
Both require management review of processes			
Both require continuous process improvement			

Both models have product quality, process focus, use of quantitative evaluation, and review and improvement as central requirements

There was general recognition in the literature that good software quality is not the norm Radding [131] identified seven steps for success for software quality These were

1 Management commitment
2 Creation of a common quality language
3 Quality as a design function
4 Building testability into development
5 A measuring quality system
6 Management and measuring of testing trends
7 Investment is automated software quality solutions

Rubey and Brewer [132] compare nine SQA standards all of which evolved from US military standards including ANSI/IEEE STD 730 [122], NATO standards, Australian and Canadian SQA standards They deduce that the degree of commonality between the various standards means that a single model can be used to comply with all the standards A summary of the requirements for an all-encompassing model derived by Rubey and Brewer [132] is produced below

1 Organization details
2 Quality assurance plans
3 Standards, practices, procedures and conventions
4 Requirements evaluation

5 Design evaluation

6 Test evaluation

7 Reviews and audits

8 Evaluation of software development processes

9 Library control

10 Configuration management

11 Subcontractor control

12 Non-developmental, non-deliverable and customer supplied items evaluation

13 Problem reporting and corrective action

14 Preparation for delivery/approval for release

15 Quality records

16 Audit of SQA

17 Rights and responsibilities of customer or contracting organisation

2 3 2 Summary of quality assessment criteria

It is important to stress that the criteria noted are taken from specific measuring tools, appraisal systems and research conclusions within the literature reported on It is not suggested that other factors are not deemed important by the referenced authors For example, although the CMM does not explicitly require a lifecycle approach, this does not mean that such an approach is unimportant to achieving improved CMM maturity levels Likewise, Crosby's maturity test does not explicitly

mention customer satisfaction, although Crosby [78] espouses the importance of this readily

The quality practices criteria in Appendix D were then summarised and reduced (table 2 3 2 1), each "sub criterion" of the appendix being either equivalent to or implicit in the main criteria stated in the table

Table 2 3 2 1 Collated and summarised quality assessment criteria

No	Main Criteria	Incorporated sub criteria from Appendix D
1	Training and development	Information and knowledge management
		Training and employee development
		Organizational and personal learning
2	Defect management	Average percent items defective
		Defect prevention
3	Cost of quality	Cost of quality
4	Customer focus and feedback	Customer focus and satisfaction
		Stated rights and responsibilities of customer and contracting organization
		Obtain data about customers
		Customer feedback driven improvement
5	Problem handling	Problem reporting and corrective action
		Formation of short term problem solving teams
6	Quality system infrastructure	Sound quality system infrastructure
		Infrastructure
		Financial, building and equipment management
7	Leadership	The role of supervisory leadership
		Top management leadership, commitment and recognition of quality
8	Communication	Communication within the company
		Creation of a common quality language
9	Quality planning	Strategic quality planning
		Quality assurance plans
10	Supplier	Supplier partnership and supplier management

No.	Main Criteria	Incorporated sub criteria from Appendix D
	management	
		Subcontractor control
		Non-developmental, non-deliverable and customer supplied items evaluation
11	Software lifecycle approach	Lifecycle approach
12	Measurement	Measurement and feedback
13	Documented quality policies and responsibilities	Explicit organizationally linked policies
		Defined roles and responsibilities
		Quality manual
14	Use of standards, practices, procedures and conventions	Use of standards, practices, procedures and conventions
15	Requirements management and evaluation	Requirements evaluation
		Requirements management
16	Reviews and audits	Management review of processes
		Evaluation of software development processes
		Audit of SQA
		Quality reviews and audits
		Design evaluation
17	Software control	Software library control
		Configuration management
		Change management and control
18	Testing management	Test evaluation
		Validation and testing plans
		Building testability into development
19	Cultural change	Cultural change
20	Quality as a design function	Quality as a design function
21	Automated software quality products	Automated software quality products
22	Teamwork, human resource management and employee involvement / motivation	Teamwork, human resource management and employee involvement / motivation
		Continuous quality improvement

No	Main Criteria	Incorporated sub criteria from Appendix D
23	Quality driven documented processes	Documented and systematic processes
		Quality records
24	Use of quality tools	Use of quality tools
25	Cycle time reduction	Cycle time reduction
26	Preparation for delivery / approval for release and product realization	Preparation for delivery / approval for release and product realization
27	Capacity for rapid change and flexibility	Capacity for rapid change and flexibility
28	Focus on the future	Focus on the future
29	Managing for innovation	Managing for innovation
30	Social responsibility	Social responsibility
31	Service provision	Service provision
32	Project management tracking and oversight	Project management tracking and oversight
33	Risk management	Risk management

The above 33 criteria were used as a starting point to evaluate the effectiveness of a quality management effort for developers and manufacturers of automated and computerized systems However, many of these 33 criteria overlapped and could be further summarised into 21 criteria as presented below

Thus, finally, the criteria used to assess quality practices were

1 Training and development

2 Cost of quality

3 Customer focus and feedback

4 Quality system infrastructure

5 Leadership

6 Communication

7 Quality planning

8 Supplier Management

9 Software lifecycle approach

10 Measurement

11 Documented quality policies and responsibilities

12 Use of standards, practices and procedures

13 Requirements management and evaluation

14 Reviews and audits

15 Software control

16 Testing management

17 Teamwork, human resource management and employee involvement motivation

18 Quality driven documented processes

19 Preparation for delivery / approval for release and product realization

20 Service provision

21 Risk management

2 4 Regulatory Practice Measurement

Derivation of regulatory related constructs was not straightforward as there was no existing literature from which to extract constructs Therefore a new set of variables had to be constructed based on themes derived from industrial literature and trade journals, elaborated on in section 2 1 of the literature review [8][9][13][40][49][50] Several factors emerged as being important for suppliers of systems in order to achieve compliance as discussed It was important for suppliers to have knowledge of the GMP regulations, and the ability to apply them to the development and delivery of their products The extent of use of the GAMP guide is also a good indicator of the compliance level of a company, although it is not suggested that compliance cannot be achieved without it The regulations apply to the lifecycle of any given automated system and require objective evidence of validation and the design approach Hence, availability of design and validation documentation from the supplier is essential Many validation features are also required to be built into systems, as it may not be impossible to test for aspects of system behaviour without these features An extremely important aspect of regulatory compliance since 1997 has been the emergence of the Part 11 This regulation has had a huge impact on the compliance requirements for suppliers of computerised systems in terms of requirements for built in capability to ensure electronic record and signature integrity A further requirement for compliance with US regulations is that the suppliers make some provision to make source code available to manufacturers, either directly or

through third party agreements Finally, the use of regulatory design reviews for software is a feature that would indicate involvement in regulatory activities These regulatory criteria were used to evaluate the extent of regulatory practices by respondents and are detailed in table 2 4 1

Table 2 4 1 Literature derived variables considered critical to regulatory practices

Regulatory Variable
Extent of direct use of GMPs in design
Extent of provision of design documentation
Extent of provision of validation documentation
Extent to which validation features are designed into products
Extent to which other regulatory requirements are designed into the software
Extent of use of the GAMP guidelines
Extent of regulatory training for system developers
Knowledge and application of rules for electronic records and electronic
Availability of source code to manufacturers
Extent of planning of regulatory activities into design
Extent of regulatory design reviews

2 5 Business performance measurement

A review of the literature revealed a number of common measures for determining business performance in survey research The requirements for this study were a set of simple common measures to all companies that were likely to be revealed by survey respondents This section first looks at the measures used in the literature, then collates them It then briefly discusses those criteria in terms of study usefulness

Rather than evaluate respondents own performance measures, which can often be misguided, global 'hard' business performance measures must be obtained according to some [133] There were a variety of performance measures in use by businesses which vary between soft internal measures such as flexibility and quality performance to hard measures such as productivity and profit and cost measures [134]

Financial measures alone may not necessarily be relied on as sole performance measures There are shortcomings with relying solely on these measures for business performance measurement particularly as they do not assess internal soft measures such as resource utilisation, flexibility, innovation and so on [135] Although not a true reflection of performance in the global sense, competitiveness and financial measures are results, which can be measured and used to determine an organisation's general performance from an external viewpoint

To follow the advice of Leandri [136], simplicity is the key to performance measurement There were salient themes found in the literature regarding how to measure hard and soft business performance

Adam et al [31] used net profit as per cent of sales, past year return on assets, and average past 3 years sales growth as business performance indicators

The dependent business performance variables used by Forker [80] were after tax return on assets, return on investment after tax, growth in return on investment, sales growth, market share, growth in market share, return of sales, and growth in return of sales These were assessed objectively by Forker [80] in a survey by asking respondents for actual figures, and also assessed subjectively by using seven point rating scales Only one third of respondents studied were willing to release actual figures

Mole and Worrall [137] used seven business performance indicators in their research Sales growth, profit growth, order book growth, export growth, workforce growth, training expenditure and business confidence were all used

McAdam and Bannister's [128] research showed that TQM could impact positively on 'hard' business performance measures although the business measures were mostly related to internal efficiency The case study research showed increase in production orders and the product range on offer over the longitudinal study timeframe These were two significant 'hard' business performance measures that could potentially have been used in a study

Lee et al [82] used net profit as a percentage of sales and annual employee turnover rate to measure operating performance and last year's return on assets, last three year's return on assets, and past three years sales growth to measure performance, in their study of the effects of quality systems in Hong Kong industry

Suggestions were given in the MBNQA award criteria booklet for possible financial measures of performance [15] These were

1 Revenue
2 Profits
3 Market position
4 Cash-to-cash cycle time
5 Earnings per share
6 Returns

For marketplace performance, the following indicators were suggested

1 Market share
2 Measures of business growth
3 New products and markets entered
4 Percentage of sales from new products

It is primarily these four MBNQA performance indicators which were used as the primary business performance criteria for this study as they can encompass many other measures

A collation of the *entire* list of business performance indicators derived from the literature is produced in table 2 5 1

Table 2 5 1 A collation of the hard business performance indicators discovered in the literature review

	Performance Indicator
1	Net Profit as a percent of sales
2	Profit growth
3	Past year return on assets
4	Past 3 years return on assets
5	After tax return on assets
6	Return in investment after tax
7	Growth in return in investment
8	Sales growth
9	Average last 3 years sales growth
10	Market share
11	Growth in market share
12	Return of sales
13	Growth in return of sales
14	Order book growth
15	Export growth
16	New markets
17	Percent of sales from new products
18	Increase in product range
19	Business confidence
20	Training expenditure
21	Annual employee turnover rate

Applying sets of these indicators to the widely used MBNQA criteria gives the derived criteria in table 2 5 2 By mapping some of the measures in table 2 5 1 onto the MBNQA indicators, a focused set of measurement criteria was acquired, which was used to form the basis for the questionnaire constructs

Table 2 5 2 MBNQA [15] suggested indicators of business performance and literature derived proposed measures for assessing the indicators

No	MBNQA Indicator	Proposed Measure
1	Market Share	Market share
2		Growth in market share
3	Measures of business growth	Net profit as a percent of sales
4		Profit growth
5		Sales growth
6		Average past 3 years sales growth
7		Order book growth
8		Workforce growth
9	New products	Increase in product range
10	Percent sales from new products	Percent sales from new products

This left a total of ten simple hard measures of business performance, which were used to develop the business criteria for the questionnaire It is not suggested that the remaining measures in table 2 5 1 are trivial, only that the above ten measures were adequate to get a realistic and attainable picture of the business performance of a system developer

2 6 Summary of literature review and derivation of study variables

The literature review looked at the pharmaceutical regulations as they pertained to automated and computerised systems and how the development of such systems must proceed in the regulated environment It looked at the area of quality management and its effectiveness, entailing a comparison and selection of a set of quality criteria that can be used to evaluate quality effectiveness in organisations involved with the development of the systems under study A set of regulatory criteria was extracted from themes in the literature Literature on business performance indicators was reviewed and a set of criteria determined to establish such performance from a survey instrument

Chapter 3: Methodology

Bell, McBride and Wilson [92] recommend the use of surveys in obtaining accurate snapshots of organisational and quality status It was important though not to end up with an attitude survey rather than a representative quality, regulatory and business snapshot Questionnaire wording and variable selection were critical in ensuring this The design of the instrument and derivation of meaningful variables was essential to a successful survey

3 1 The survey instrument

This research used an e-mail questionnaire in conjunction with a web based survey and an option for postal submission by respondents The use of such survey methodology has been addressed in the literature It must be said however that as time goes on, e-mail usage and familiarity increases in all sectors of life Thus some of the earlier research findings in the literature may no longer be entirely transferable to contemporary settings

There is evidence from the literature of an increase in the use of e-mail in survey research [138] The advantages associated with e-mail surveys are its capacity to allow processing of large amounts of information and to increase interaction

between researchers and respondents [139] However, there are limitations in terms of response rates, which ranged from 1% to 6% [139]-[142]

The target audience is very important in survey research, particularly so in e-mail surveys, as the requirement for routine and established Internet and e-mail usage by the respondents is vital By selecting a group (as is the case in this work) that uses e-mail as a core part of its business then higher response rates should be expected

The important factors attributed to low response rates by Ranchhod and Zhou [139] were

1 The inherent lack of anonymity by using e-mail
2 The lack of formality that may be attributed by some to e-mail
3 No incentives offered to the respondents such as prizes or research results
4 The layout of the e-mail in terms of its aesthetics and flexibility of use

Schaefer and Dillman [143] reported on the response rates achieved in various research surveys In most cases postal survey response rates were larger than for e-mail surveys They collate the published factors attributed to the low response rates and formulate a standard methodology This methodology however involves inserting the actual questionnaire into the text of the mail message rather than the more favoured method of using the e-mail to point to a web site as described by Klasson and Jacobs [144] The speed of e-mail fared better than for postal mail in all

cases where this was reported The number of times that a respondent was contacted also had a positive bearing on ultimate response rates The main features of the standard method suggested and used by Schaeffer and Dillman [143] were

1 Pre-notification of intent to survey
2 Personalisation (using the persons name rather than a 'dear sir')
3 Thank you mails and reminders
4 Provision of replacement questionnaires
5 Careful design of the page to reduce cognitive effort on behalf of the respondents
6 Users must simply send a reply to the researcher and populate the response email with X's and answers to open ended questions
7 Option to return by post
8 Repeat contact
9 Non-use of the Carbon Copy or Blind Copy functions of e-mails to ensure mail is not perceived as spam mail

Their experiment using this methodology yielded much improved response rates from that in previous literature as reported in their paper Response rates between 8% and 73% have been reported dependent on the target population Average rates were reported from the literature as 23 5% for single contacts and 41% for two contacts, and even greater again for three contacts Mixed mode studies using a

combination of both email and postal questionnaires could also help boost response rates [145]

The use of new technologies in survey research has the potential to introduce respondent bias In e-mail surveys these may be related to the computer literacy of the target sample, the availability of e-mail of target respondents or company policy for responding to e-mail [144] Access to web based technology and available resources for completing questionnaires may favour larger firms E-mail questionnaires offer advantages in terms of turnaround speed and international access It may also be possible to carry out censuses of entire international populations in ways that would not be practical for postal surveys On the assumption that e-mail and Internet access is freely available to the researcher, the cost advantage over postal surveys is important Ease of follow up and the ability to thank respondents are also advantageous [144] E-mail can be used in three ways Firstly, by inserting the questionnaire into the e-mail text, secondly by attaching a questionnaire to a mail, and thirdly by providing a web link on the e-mail which hyperlinks onto a web survey page When using attachments, consideration must be given to the file format of the document Several types should be considered Using web software makes collection of data easy A disadvantage though is that unintended respondents can access the web and fill in the questionnaire Web based surveys are likely to succumb to the same 'survey fatigue' as other types of survey, leading to reduced response rates [146]

Trust, cost and rewards are three critical considerations when designing the instrument The trust of the potential respondents must be obtained Costs to the respondents (in the form of time and resources) should be consciously minimised and some form of reward or incentive should exist to encourage respondents This may be in the form of an offer of the results of the research findings Advanced contact and follow-ups both assist in achieving a worthwhile response rate Some research suggests [140] [147] that e-mail response rates were not as good as for paper based postal surveys However the use of self-selected groups or convenience samples [143] [148] can enhance response rates Klasson and Jacobs [144] suggest therefore that sending questionnaires to a random sample may not be beneficial However, care has always to be taken to ensure that a convenience sample is a representative one which will not introduce bias

From reviewing the literature it was clear that electronic administration of a questionnaire was an acceptable means of survey research, particularly when an international reach was required The guidelines and methodologies suggested by Schaeffer and Dillman [143] and Ranchhod and Zhou [139] were adhered to as much as possible so as to maximize coverage and respondents, hence attempting to avoid non-response bias It was hoped that familiarity in computing technology by respondents would be advantageous and would yield higher response rates than forecasted by the literature

3 2 Sampling strategy

The sampling frame consisted of the selection of suppliers of automated and computerized systems found in the *Pharmaceutical Technology's Buyers Guide* [11] The guide represented almost two thousand suppliers of all sizes and relevant product types from which a qualified survey population was selected consisting of original equipment manufacturers and system developers Suppliers from all sectors including materials, contract analysis and laboratory services were included in the guide and were not relevant to this work

The buyers guide had an international reach and claimed to have 80% coverage of worldwide suppliers to the pharmaceutical industry This figure is statistically based as stated by Pharmaceutical Technology [149] There is no evidence either way to suggest that the remaining 20% of suppliers have characteristics any different from the proportion of the population included in the guide Therefore it was assumed that the 80% of suppliers would adequately represent the population

E-mail addresses were acquired from the Internet for every potential respondent and a database was compiled consisting of these addresses and the supplier's names No distinction was made between large or small companies or the types of products produced, once each supplier could be placed in the category 'develops automated or computerised systems for use in pharmaceutical manufacture'

Suppliers from the other major journal, *Pharmaceutical Engineering* [38] were used both to validate the 80% claim of *Pharmaceutical Technology* [11] and also to top up the list of available respondents

The entire sampling frame was then considered to be applicable to the study and all were used to create the database of potential respondents for the survey

3 3 Questionnaire administration strategy

The survey questionnaire was pre-tested by university staff and by selected suppliers to the pharmaceutical industry, and then piloted to a group of randomly selected respondents after modifications based on the pre-test The returned questionnaires were then used to adjust the questionnaire template for the main study This was then administered to the complete sampling frame The methodology and guidance provided by Schaeffer and Dillman [143] and Ranchhod and Zhou [139] was followed This resulted in the following administration strategy

1 Pre notification of intent to survey by targeting rather than sending to a large group of collected e-mails
2 Where possible, acquisition of names of agreed respondents
3 Provision of an attached MS word questionnaire
4 Option to post the responses by paper mail
5 Option of using an instant link to a web survey

6 Offer to release the survey findings to the respondents on completion of the research, which would have competitive advantages

7 Repeated contact

8 Provision of replacement questionnaires when requested

9 Thank you mails and reminders

10 Complete anonymity for respondents This would mean that it would not be possible to link suppliers to their survey responses This was assured by using the web-based survey host and by extracting data from questionnaires returned by e-mail Hence associations between respondents and data was not possible once the data was entered into SPSS Assurances of anonymity were provided on all e-mail correspondence, the questionnaire instructions and on the questionnaire itself

Targeting can help to improve e-mail survey response rates but care should be taken not to introduce bias to the survey [150] Targeting involves individual communications to potential respondents as distinct from sending mails to a list, which can be interpreted by targeted organizations as spam and treated as such A form of targeting was used here using carefully constructed emails, an identical mail being sent to each potential respondent individually

The questionnaire was carefully designed to ease completion and reduce effort whilst maximising the probability of response Guarantees of anonymity were

provided throughout on all e-mails and the questionnaires The university e-mail system was used to assure respondents of the credibility of the study

3 4 Building the Database

The aim of building the database was to produce an international list of potential respondents, including contact details Firstly it was thought that a single database (Pharmaceutical Technology's (PT) Buyers guide [11]) would result in a sufficiently large and thorough study frame However through validating this with the Pharmaceutical Engineering (PE) suppliers listings (from the ISPE) [38], it was found that only seventy percent of the test list from PE were found in the PT database The test list was made up of all advertising listings in PE over a three-year period from 2002 to 2004 inclusive

Also, the PT database yielded just 452 potential respondents Adding the qualifying companies from PE and those found from other online databases [151]-[153] increased the number of potential respondents up to 647 A very small percentage (not measured) of the companies included in the databases searched had no Internet site or e-mail address These were rare however and deemed small enough in number that their exclusion from the study would not introduce any significant non-response bias It was hoped that over 100 responses would be obtained leading to a response rate of 15% which would be high for an e-mail survey and would require an aggressive and well managed survey administration

Each respondent's website was searched to ensure that they produced systems for use in a pharmaceutical manufacturing market, or that it was quite feasible that the products on offer could be used as such (this was supported by the fact that they were sourced from a pharmaceutical database) A second criterion was that the products had some level of automation This was generally very obvious but in some cases the product specifications were assessed or occasionally, the manufacturer was contacted The website address and the e-mail addresses were entered into the database

Where it was found that companies were part of some global family of companies under a single umbrella company, a determination was made as to the independence of the sub-companies (usually evident through independent websites or independent premises) The sub-companies whose independence was clearly determinable were included as separate entries in the database (Where independence was not determined, only the parent company was included in the database)

All available e-mail addresses were input to the database In many cases the addresses were sales addresses The administration procedure used ensured that many of the addresses were used for first-contact purposes and as conduits to the preferred targets, Quality managers Many of the sites did not provide e-mail

addresses but online forms instead Again, these could be used as conduits to obtaining access to the target questionnaire completion personnel

Once the database was compiled, the potential respondents were contacted by e-mail The purpose of the first contact e-mail was to get agreement from respondents as to their participation in the study A standard e-mail template was used and a series of response e-mail templates were also employed (Appendix A 1) Also, a mail template was utilised for non-response follow-ups (Appendix A 2) That is, where no response was obtained a follow-up was sent approximately two weeks after the first enquiry Once responses were obtained from the follow-ups, the original first contact template mail was again employed to inform respondents as to the nature of the study

The first contact mail gave an overview of the study, stressed the importance of getting a high number of respondents and asked the addressee of the mail to participate No carbon copying or broadcast e-mailing was used This would ensure that mails were not mistaken for 'spam' or nuisance mail The central philosophy of the database-building phase was to try and build relationships with respondents by e-mail so as to attempt to maximise the likelihood of receiving completed questionnaires

The e-mails were sent over two different time frames This had two purposes Firstly it meant that response mails could be managed easier allowing more involved

contact with each respondent Secondly it would help ensure that there were no temporal underlying factors affecting the response rates The first batch of mails involved 375 entrants A total response rate of 52% was (eventually, see below) achieved Of these, 142 or 38% agreed to participate Agreements varied from those who wholeheartedly wished to participate to those who would 'have a look' at the questionnaire and make a decision afterwards All respondents were thanked Those who agreed to respond were sent another mail to let them know that they would be contacted again regarding the questionnaire, once the instrument had been pre-tested

It was found that very few responses were returned after the initial mailing The second mailing, which stated that there had been no response to the first mailing, yielded a much higher response rate Third and final mailings (a repeat of the first mailing) yielded some success too It was decided that as a rate of 38% (achieved after the initial mailing, a reminder and a repeat of the initial mailing) considerably exceeded the overall requirement of 15%, and as responses were unlikely from those who had not made any contact at all, no further mailings would be sent It is hence a finding of this study that adequate response rates using e-mail surveys could be achieved using a starting mail and two follow ups It should be said however that in the pharmaceutical industry, suppliers are used to receiving assessments (which often take the form of a questionnaire) by e-mail This might account for the high initial response rate relative to that reported in the literature as being typical for e-mail responses

There were no apparent response patterns from the first mailing lot The respondents appeared varied in terms of regulatory environment, organizational size and end product type From this there was no evidence or reason to believe that any bias was present However, background information gathered from the questionnaire would be necessary to clarify and assess respondent characteristics The sampling frame itself, as derived from the database, was almost a census frame for the defined respondent profile Therefore as there was an equal chance of each respondent replying (all were contacted), and no clustering or stratification took place, the sampling could be considered to approximate simple random sampling As such, no obvious bias was present in sampling and hence no obvious threats existed to the external validity of the study

3 5 Questionnaire design

3 5 1 Methodology

The questionnaire was developed through a number of phases Initially a set of questions was drafted which linked to the study variables and to required background information In the main, the questions were new to this study The questions were designed so as to ensure that they were clearly representative of the measure which they purported to represent, thus giving maximum assurance of content (face) validity

After carrying out an initial reduction of the instrument (from a large number of possible questionnaire items, to a smaller number of representative items), a pre-test was carried out The pre-test was carried out by contacting 5 potential respondents from the study database to form a focus group Some of the pre-test participants were those who had expressed an interest in the proposed survey methodology or in the outcome of the study when compiling the respondent database initially Once agreement was achieved a set of instructions was prepared (see appendix A 3) for the pre-test The instructions for the pre-test prompted the respondent to critically appraise the questionnaire in terms of content, appearance, difficulty and validity The quality, regulatory and business performance variables identified in Chapter 2 as well as the background variables identified in section 3 5 3 were also listed as an appendix to the pre-test instructions

A spreadsheet was created using all the variables from the study Every variable was then considered separately Constructs were introduced to represent the variables based on constructs extracted from the literature or new questions were proposed that had a strong relationship with the variable Some of these questions (constructs) had to be created anew whereas others were based on themes from the literature For example, in the case of the Human resources variable, the literature in general states (or merely intimates) that the existence of goals and objectives is a consideration that contributes to the strength of human resource management Hence this consideration was translated into a question that could be used to assess

the variable That is, where there are no obvious constructs available, they were derived or extrapolated from the general body of literature All questions were later evaluated for their relevance and value to the variable that they would represent Groups of questions were assessed as to their comprehensiveness towards covering all that would be required to get a realistic picture of how the respondents performed with respect to each variable Questions were then added or deleted as required

The questions themselves were left sufficiently open (linguistically and methodologically) so as to be relevant to as many respondents as possible That is, specifics were avoided where not required so as to not to preclude differences in respondents approaches to each variable This might have an equally beneficial effect and become masked were too much direct and specific questioning posed Vagueness and ambiguity was reduced through retrospective analysis of each construct so as to improve the instrument's reliability A relational analysis was carried out between constructs to reduce the amount of questions asked by comparing the intent of the questions, and combining them or removing them depending on their determined exclusivity Supporting questions were added or questions revised where possible ambiguities were perceived Finally a set of questions were produced relevant to each variable which were deemed to be of sufficient value and independence to warrant inclusion in the questionnaire to be pre-tested 'Nice to have' questions were eliminated and only required ones were used so as not to have a questionnaire that was too large and cumbersome It was

important to have an instrument that was accessible and did not overburden respondents This would have been detrimental to the volume and quality of respondent data received

A checklist was prepared before pre-testing which assessed the questionnaire item by item The checklist was based on several texts on preparing questions and questionnaires for use in survey research [154]-[157] The questions for acquiring factual type information usually used four to five point ordinal multiple-choice questions whereupon ascending answers on an ordinal list would indicate the respondent's strengths in a particular area For opinion or belief type questions Likert-scale related items were used to assess the respondent's position Odd and even ordinal-scaled items were used to avoid potential central tendencies in some cases (even) and to allow neutral options in some cases (odd) The use of open-ended questions was minimized (only one appeared in the final questionnaire, which went largely ignored by respondents)

The checklist was used to assess the general appearance of the questionnaire, its length, user friendliness and layout Each individual question was then assessed under several headings as derived from the survey research methodology literature

1 Is the question simple?

2 Is the question clear?

3 Is the question manageable or does it involve burdensome tasks?

4 Does the question contain concepts or nomenclature that may not be in common use?

5 Does the question have any ambiguities or does it use any potentially shared definitions?

6 Is the question specific enough?

7 Is the question stand-alone? Would any definitions or assumptions be required?

8 Does the question help to exhaustively assess its related variable?

9 Is there any order interference (that is, will the answer to a question be influenced by the answer to the previous question) associated with the question or could it potentially introduce any order interference?

10 Is the question leading? Does it allow for swings in opinion / position and does it allow for any potential neutrality?

11 Could the question be combined with another?

12 Are there sufficient residual 'others' available to the respondent?

13 What is the real value of the question? What if it were deleted?

Considerable work was then carried out to the appearance of the questionnaire and the instrument was prepared for pre-testing At this stage the instrument consisted of 134 items and was 10 pages long after considerable attempts at reduction without causing excessive bunching of questions The questionnaire was prepared in Microsoft Word™ format only Several drafts were produced until a satisfactory final pre-test draft was produced

3 5 2 Structure

The questionnaire was laid out so as to be clear as to what each section was attempting to do It was titled 'Survey of quality practices, regulatory practices and business performance for developers of automated systems for use in pharmaceutical manufacturing' The title was so worded as to immediately indicate the full scope to the respondent, attempting to ensure that they would not respond if their activities were not inside the scope (which was clarified later in questionnaire instructions and in the e-mail correspondence with respondents in any case) A header was then presented emphasizing the value of returning the completed questionnaire due to the limited population of potential respondents, and assurances of confidentiality Supplementary to this, the value of the findings of the study to respondents was outlined, and instructions for obtaining the results were provided A statement was initially included which informed the respondent that input from more than one organizational department was likely to be required

The following sections were used in the questionnaire

I Background and qualifying questions

II Organizational Management

III Quality Management Systems

IV Regulatory related practices

V Software quality related practices

VI Business performance

Section one originally consisted of mostly open-ended background questions used to qualify or support the quality, regulatory and business data In general, these questions were not related to variables but could be used to understand findings Questions included those which attempted to assess company size, complexity of code, perceived criticality of products in terms of drug quality and so on as discussed in section 3 5 3 Sections II to VI asked questions with direct association to one of the study's variables They, with the exception of section V, were all originally 6 point Likert-scale questions preceded by the statement 'to what extent can it be said of your company that ' Most of these questions had distinctive closed ordinal options relating to the variable rather than Likert-type 'strength of opinion' items This was to ensure that factual, more objective information was obtained where possible rather than the more subjective attitudinal type responses characteristic of Likert scale related items Section VI on the other hand asked for estimates relating to business performance No absolute figures were required in this section originally, just percentages An emphasis was presented on provision of comments, and initially it was requested of respondents that they would provide alternative hard financial data, where the requested options on the questionnaire for business performance were not relevant This was because it was expected (and evident from the literature) that business performance measures would differ considerably between respondents, which may be due to many factors, of which geography (in terms of what market the respondents supply) was likely to be one At

the header for each section a description was given of what was meant by each possible selection on the Likert scale related items This ranged from 0 = 'Not at all' to 5 = 'To a great extent' An explanation of the purpose of the section was also provided in the header For each option, instructions were provided which instructed the respondent to place an 'x' in the box Alternate questions were highlighted in grey to provide clear visual delineation between questions, hence avoiding errors and aiding clarity

3 5 3 Background Variables

In order to avoid threats to external validity, it was important to establish the context in which the respondent's data was set In order to do this, background variables needed to be measured in the questionnaire The length of time a company is in business may potentially have an impact on the scores obtained from respondents It was not sufficient just to look at time in business, as it was possible that a company in business for many years may be recent entrants to the pharmaceutical market Hence, it was also necessary to determine how long an organization had been active in the pharmaceutical market Similarly, it was necessary to establish company size, which could have had an influence on scores

The regulatory and quality environments that respondents operate had to be determined, in order to ascertain whether differences existed between respondents in differing environments, and whether generalisations could be made The same applied to the complexity level of the software used in the respondent's product, and

how critical that software was to the end user's drug quality That is, more complex or critical software may lead to more stringent controls and practices by suppliers As complexity of software is a difficult thing for respondents to categorise, the time taken to develop software was used as an indicator for measuring complexity, where low complexity software was that which took in the order of a few months to develop, and high complexity software took many months or even years to develop

It was initially anticipated (but removed after pre-testing), that it would be useful to determine the effect that regulatory and quality changes had on the end prices of products However, these variables were not consistent with the objectives of the survey

Many companies develop software at the manufacturer's site and use the in-house quality system to do so Hence it was asked whether the developer fell into this category, and to what extent they used an independent quality system It was also initially suggested that it would be necessary to determine whether the company wide quality system applied to the software development environment This was eventually removed from the questionnaire, as it was clarified in the survey instructions that the questionnaire applied to the software development environment

Finally (post pre-study) two additional background variables were added The focus of these was to determine if there were differences in scores between companies who had experience with audits by their pharmaceutical customers, or whether those

customers asked for quality plans. This direct involvement with the pharmaceutical industry may have driven supplier behaviour and practices.

The final background variables considered are hence detailed below.

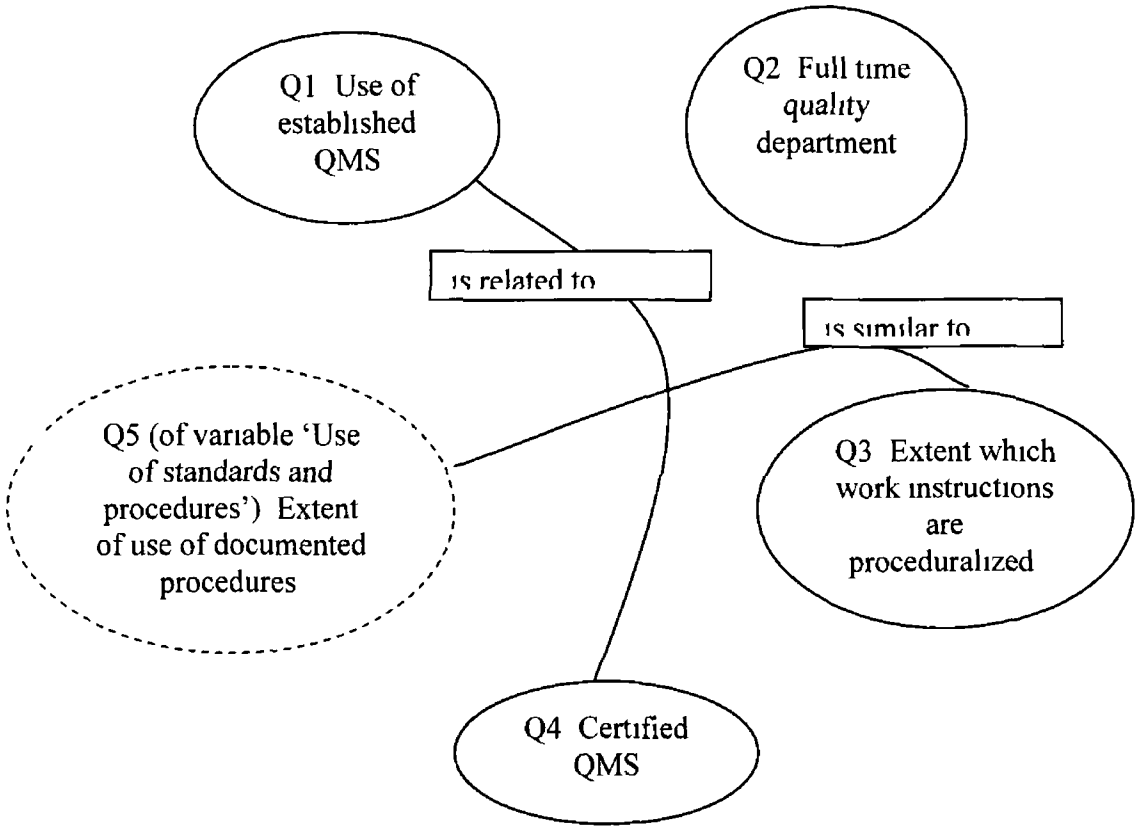
1. Length of time in business
2. Length of time serving pharmaceutical industry
3. Company size
4. Complexity of automation used in products
5. Regulatory environment
6. Extent to which supplier is subjected to customer audits.
7. Extent to which supplier is asked for a quality plan from customers.
8. Criticality of product to drug quality.
9. Organisation type.
10. Quality system independence from client.
11. Quality management environment.

Note that the international focus was not ascertained through looking at the country of origin of the respondent, but rather at the market they were supplying. Hence the questionnaire asked about whether companies sold into FDA, EMEA, PIC/S, WHO or other markets. The reason for this is that it was felt it was not the country of origin of the supplier, but the country of drug manufacture (regulatory environment) which makes the difference in terms of supplier practices. This has been observed in practice by the author with pharmaceutical suppliers.

3 5 4 Initial reduction and justification of questionnaire items

In order to ensure that each question added independent value to the study, that sufficient constructs existed to allow evaluation of the variable represented, and that questions were worded clearly and unambiguously, an initial analysis was carried out of the survey instrument A phased approach was taken whereby a relational diagram was produced showing all constructs representing a given variable contained in individual bubbles The relationships between the constructs were drawn Relationships to other constructs relating to other variables than the variable under analysis were also constructed Reduction then took place by means of a qualitative evaluation of the independent value of each construct (that is, what unique contribution it would offer) and of the commonality between constructs After reducing the list of constructs to those that added high value to the variable, an assessment was made as to how thoroughly the variable was served by the remaining questions In some cases, supplementary or clarification constructs were added to support the variable or another construct In the end the number of questions to be asked was only slightly reduced Figure 3 5 4 1 (for illustration only) below shows an example of a relational diagram and the qualitative evaluations used to reduce the amount of questions and to assess the thoroughness of the construct set

Variable Quality system infrastructure



ANALYSIS

Question 1 is related to Question 4 As a certified QMS is an indication of the use of an established QMS, then Question 4 can be considered to add little value to the variable as they essentially ask the same thing Therefore Question 4 will not be used

Question 3 is similar to question 5 for the variable 'use of standards and procedures' It is much more closely tied to that variable and will not be asked for the infrastructure question

The combination of questions (1, 2,) provided adequate coverage for the variable

Figure 3 5 4 1 Illustrative example of how relational and coverage analysis was carried out

For the open type questions in section I, relational analysis was not used (except for those cases where the question was linked to a variable) However, a qualitative assessment was carried out which examined the structure of the questions This caused improvements in clarity and form In general this resulted in a move to more closed type items

3 5 5 The Pre-test

The next stage of reduction was the pre-testing Five respondents who had agreed to complete the questionnaire were selected based on their unsolicited stated interest in survey research Although these five had many of the characteristics of a focus group they did not contact each other at any stage They remained anonymous from each other Independent assessments of the questionnaire were also sought from two people who had no experience in survey research or the focus of the study This was to get non-expert opinion as to the appearance and user-friendliness of the questionnaire Appendix A 3 shows the pre-test instructions sent out with the draft questionnaires A set of questionnaire completion instructions was also sent to the pre-testers The pre-test instructions asked the respondents to feel free to criticize, enhance or make suggestions to improve the instrument in whatever way they chose It stated the purpose of the questionnaire clearly and asked the respondents opinions as to whether they believed that the questionnaire addressed what it was supposed to (i e the questionnaire was internally valid) The study variables and background variables were presented as an aid to the pre-tester in

determining the suitability of the questions The respondents were asked to appraise both the questionnaire and the instructions Prompts were provided in the form of 9 questions addressing the simplicity, clarity, difficulty, ambiguity / specificity, burden, accessibility, relevance to study questions and variables, and the feelings of the respondent regarding the completion of the business performance questions This was asked because concerns existed over the intrusiveness and confidentiality of proprietary financial information It was important that business performance data was acquired in order to answer the research questions

The pre-test resulted in the following findings

1 The questionnaire was too long 10 pages and 134 items were thought to be excessive and unlikely to result in obtaining sufficient data
2 The questionnaire looked unprofessional Recommendations were put forward for comparing the instrument presentation with some professional surveys used for marketing purposes, credit card companies and other such bodies
3 The use of an online survey option was highly recommended to improve response rate and accessibility (at this point, only the MS Word version was known to respondents)
4 More 'neutral' and 'residual other' type options were required in general and in some specific cases That is, some of the questions forced a leaning in a certain direction, where a neutral question would have given respondents an opportunity not to lean in either direction The addition residual other questions would allow

respondents to opt out of an answer, where the question had no relevance to their business

5 The business performance section of the questionnaire was intrusive and difficult to answer, and unlikely to encourage a high response rate

6 The questions in some cases were unfairly predisposed to a particular direction This was particularly the case for the business performance section where questions were asked relating to how much certain facets have increased or grown with a lean towards growth rather than decay or neutrality

7 To assess the respondent's 21 CFR Part 11 scores, it was pointed out that the questionnaire did not adequately address the underlying features of part 11

Each of the main comments was addressed in some way and led to an overhaul of the questionnaire Through vigorous application of the literature-derived checklist in section 3 5 1, and a variable reduction phase, the number of questions was reduced from 134 to 84 This resulted in a 7-page instrument An affordable online web-survey host [158] was located and the questionnaire was built and launched as an online form Considerable work was done to the appearance of the MS Word™ questionnaire to improve the flow and aesthetic features Comparisons were made with various postal surveys received through junk mail and on the Internet Neutral and residual other options were provided where suggested and the other questions assessed as to whether such options were required The Part 11 variable would be assessed with a more in depth set of constructs These would measure the

respondent's practices with regard to the actual requirements of Part 11 electronic signatures and records, security, access and audit trails

In order to aggressively reduce the number of questions to a manageable but still useful number, the study variables for quality practices were evaluated as they were the most numerous (21) The purpose of this exercise was not to diminish the importance of the variables derived during the initial literature evaluation but to see if a variable could be measured as subsets of other variables A table was created with all the variables present together with the literary references for each variable presented in columns A 'literary importance' score was again produced based on the amount of times the particular variable was deemed to be important in the reviewed body of work That is, if a variable was stated as being important in 6 different papers (reviewed as part of this work), then the variable received a literary importance score of 6 A series of questions was then produced as an evaluative tool, which looked at each variable

1 What is the literary importance score for the variable?
2 Could the variable be considered a sub-category of another variable?
3 How independent does the variable seem from the other variables?
4 Could the main score (quality practice / regulatory practice / business performance) stand up without the inclusion of this variable (i e would the combined set of items provide a valid score without the variable?)

5 Write some general comments on the value of the variable in light of questions 1 to 4 and on omission of the variable

6 Make a decision on whether to retain or remove the variable from the study or whether to subsume the variable into another variable

Table 3 5 5 1 shows the resultant evaluation for the set of quality practices study variables that were eliminated at this point and the decisions made

Table 3 5 5 1 Quality variables removed for the purposes of instrument reduction during pre-testing

Variable name	Literary score	Number of associated questions in original questionnaire	Rationale for removal
Testing management	4 (30%)	3	Testing management can be considered a work practice and can be assessed as part of the variables that assess whether work processes are well documented and followed The literary score was low
Cost of quality	2 (14%)	2	The low literary score was the main reason for exclusion As only 14% of the literature surveyed indicated COQ to be amongst the most important criteria in quality success, then it was reasonable to propose that the remaining variables would provide an adequate indication of the quality practice strengths of the respondents
Preparation for delivery / approval for release and product realization	2 (14%)	1	Same rationale as for COQ

Variable name	Literary score	Number of associated questions in original questionnaire	Rationale for removal
Risk management	2 (14%)	1	Same rationale as for COQ

The regulatory variables were also looked at in the same way as the quality variables with the exception of the use of the literary score technique This was because the regulatory variables were derived from professional literature that was not generally research based and the constructs were developed from a summation of the literature rather than a cross examination The eleven regulatory variables were reduced to nine Table 3 5 5 2 below shows the decisions for removal of two regulatory variables from the study

Table 3 5 5 2 Regulatory variables removed for the purposes of instrument reduction during pre-testing

Variable name	Number of associated questions in original questionnaire	Rationale for removal
Extent to which *other* regulatory requirements are built into the software	1	It was sufficient to measure whether GMP (and hence all regulatory requirements) is built into the respondent's products This could be more than adequately addressed by the 'Extent of direct use of GMPs' variable
Extent of planning regulatory activities into design	1	It was really the end goal that was important with this variable, i e that regulatory activities are part of design The planning should be the means by which it was achieved but for the purposes of the study it was sufficient to measure the end goal

The most fundamental changes to the questionnaire as a result of the pre-testing were in the business performance section The literature was consulted extensively and new measures and constructs were produced which were more likely to provide business performance data through a questionnaire The questions were adapted from the work of Luk [159], Kannan and Tan [160], Greenley and Foxall [161] and Rozenwig [162] although they were tailored to suit the focus on the pharmaceutical industry for the purpose of this study The measures were mainly consistent with the business performance criteria derived during the initial literature survey, although the means of acquiring the data differed substantially The remaining measures as used by previous studies to determine business performance were

1 Change in market share over 5 years in the pharmaceutical industry
2 Overall profit levels for products sold into pharmaceuticals over 5 years
3 Overall sales volumes into the Pharmaceutical industry over 5 years
4 Overall percentage sales from new products (pharmaceutical) in last year
5 Competitive strength relative to competitors

For the first 4 variables subjective closed measures were used asking the respondent to select on a 5-point scale whether their results were considerably below expectations, below expectations, met expectations, exceeded expectations or considerably exceeded expectations For the relative competitive strength variable, a 2-item Likert scale was employed

The use of measures that may be deemed to be partially subjective, to accurately reflect objective realities, is supported by the literature [159] - [162] Although not as effective as acquiring objective data, strong correlations were found in the literature between subjective and objective measures making the use of subjective measures acceptable [163] - [165] From the pre-test it was evident that getting objective proprietary data would be a barrier to high response rates

As these measures were found to produce valid results in other studies, which used questionnaires to measure business performance, they were deemed adequate for use in this study Although fewer variables were employed than initially set out from the initial literature review, the main elements of the original variables (Market share, Profit and profit growth, sales and sales growth, and new product sales) were covered in the five variables selected above, with the exception of 'Workforce growth', which was not assessed

After completion of the pre-test remedial work the questionnaire was reconstructed both in the MS Word format and on the online version The pre-test respondents were again contacted and presented with the new questionnaires Some minor adjustments were made and the pre-testers were satisfied with the revised instrument The questionnaire was then 'locked down' as a single controlled soft copy in preparation for Pilot testing

The resultant and final questions were those presented on the questionnaire in Appendix B 1

3 5 6 Pilot testing the instrument

The questionnaire was sent out to twenty respondents who had agreed to take part in the study (as determined by the database building) The respondents chosen were the first 20 in alphabetical order in the database Therefore, no particular respondent characteristics were chosen In addition to these 20, a further 21 respondents, who had made contact after several reminders had been sent, were also given the questionnaire to complete From the 41 sent, 29 questionnaires (71%) were either returned or completed online The e-mail instructions (appendix B 2) were sent together with the final questionnaire (appendix B 1) and a web link (URL) The instructions stated that the questionnaire was focused on the respondents software / automated system development environment and provided 3 ways to complete the questionnaire, online, by completing the MS Word™ document and returning by e-mail or by printing out and completing the MS Word™ by hand, returning by normal mail The instructions also contained statements of confidentiality, anonymity and non-disclosure The respondents were not made aware that the questionnaire was being pilot tested but were asked for comments on the questionnaire

In general, the questionnaire was well received and comments were mostly positive with regards to presentation and ease of completion Some suggestions were made regarding removing forced choices on the online questionnaire to allow respondents to choose whether or not to answer certain questions This was taken into account and the online questionnaire was modified accordingly Some other minor modifications such as adding residual others also took place but in general the questionnaire remained unchanged This also meant that the 29 valuable respondent data sets could be used in the full study

The most important finding from the pilot study was that some of the respondents who had agreed to participate in the study initially had forgotten Therefore when they were sent the questionnaires they did not respond and needed to be reminded about it The lesson from this was that in the main study, 'memory jogging' mails would be sent out first and agreement re-established before sending the questionnaire and instructions

The pilot response rate of 71% was higher than expected and much higher than what the literature pointed to as being a reasonable expectation This was the case even though the same best administration practices from the literature, which reported much lower response rates, were followed As a total of approximately N=100 would be required to make the study meaningful and representative (externally valid) and would allow analytical tools such as factor analysis to be applied with confidence, the administration strategy was retained for the main study

The high response rate was probably attributable to the use of that strategy combined with the high emphasis on repeated personal informal communication with respondents and also to the fact that respondents seemed used to answering questionnaires This was possibly because many of them had participated in supplier assessments, which often use questionnaires to evaluate supplier quality practices in the pharmaceutical industry

3 5 7 Analysis of the pilot study data

The pilot data (with N=29) was analyzed using various SPSS statistical procedures The data was mostly ordinal and where possible non-parametric tests were employed which did not make any assumptions of normality or continuity In some cases though parametric testing was used in order to harness the power of such tests to determine differences or relationships between ordinal variables It has been widely argued in the literature that the use of parametric testing for ordinal data is acceptable [166][167] The main study variables certainly had the characteristics of continuous normally distributed interval variables as the high number of intervals present in the data made it very close to continuous even though the variables were derived from ordinal sources (see below) Visual checks using SPSS plots and tests for skewness and kurtosis for the main variables confirmed normality for the three variables Quality, Regulatory and Business (Table 3 5 7 1) Kurtosis and skewness values of less than +/-1 indicate acceptable normality, with zero representing perfect

normal distribution This allowed use of parametric testing, for the purposes of the pilot study, to evaluate relationships between these three variables

Table 3 5 7 1 Normality statistics produced for the three study variables showing normal distribution

		Quality	Regulatory	Business
N	Valid	29	28	29
	Missing	0	1	0
Skewness		033	- 423	002
Std Error of Skewness		434	441	434
Kurtosis		- 147	569	- 206
Std Error of Kurtosis		845	858	845

The individual scores from each question were all standardized to give equal weighting to the sub-variable it was designed to represent They were then summed to form a scaled sub-variable The reliability of the questionnaire items within the scale was then checked using Cronbach's Alpha The coefficient alpha values for the pilot study data sub-variables and their corresponding questionnaire items are presented in appendix C 1 Some items had to be removed (only for the pilot study) to ensure reliable scales were being employed In the main however, reliability was confirmed Ideally alpha values of greater than 0 7 are acceptable For the pilot study this was mostly achieved however some scales were accepted with coefficient alphas below the recommended 0 7 threshold This is a regular occurrence in the literature [159][161][167] It would have been detrimental from an information-gathering point of view to remove some indicators where reliability was not ideal but still adequate The decision was hence made to retain some less than ideal scales for the pilot study

The sub-variables were related to the three main study variables of quality practices (Quality), regulatory practices (Regulatory) and business performance (Business) Two approaches were taken to reducing the number of variables to a more representative sub-group of main study variables Ideally, factor analysis would be used This was attempted but the small N meant that very low communalities were noticed and the number of factors extracted using principal components analysis which would even reasonably explain the variance, and hence represent the sub-variables adequately, approached the number of sub-variables themselves So the factor analysis was not used here

The second technique was to use simple summated scales (See appendix C 1) Here, a set of sub-variables would be scaled to produce a score for quality, regulatory and business performance Firstly, the reliability of the items making up the sub-variables had to be ascertained Each sub-variable was represented by a number of questionnaire items Cronbach's alpha was used to determine if the items 'varied together' and could be used to form a sub variable Items were removed until a reliable scale was achieved Appendix C 1 shows what items were removed to form the sub-variables These items were then summed to produce a sub-variable score The sub-variables (which consisted of sub-variables that had a single questionnaire item and those which were analysed in appendix C 1) were then assessed as to whether they varied together to form a scale, which could be used to represent the main variables The sub-variable scores could then be summed to produce a single score for quality, regulatory and business performance The

reliability of the sub-variables scaled was tested using Cronbach's alpha and in the case of the set of Quality sub-variables (Table 3 5 7 2), Regulatory sub-variables (Table 3 5 7 3) and Business sub-variables (Table 3 5 7 4) was found to be reliable as coefficient alpha exceeded 0 7 or was deemed sufficiently close to 0 7 to be useful In all cases, the sub-variables were equally weighted into the scale, each sub-variable score had a maximum of 1

Table 3 5 7 2 Scale reliability for Quality sub-variables

	Cronbach's Alpha if Item Deleted
TrainAndDevelop	833
TeamworkHR	839
CustFocus	837
Leadership	836
Communication	834
QualPlanning	830
DocQualPols	835
UseStandPracProc	834
ReqManagement	832
ReviewsAudits	827
QualDrivenProcesses	829
Measurement	848
ServProvide	844
QualSysInfrastructure	851
SupplierManage	838
SoftControl	870
LifeCycle	875

Reliability Statistics

Cronbach's Alpha	N of Items
849	17

Table 3 5 7 3 Scale reliability for Regulatory items

	Cronbach's Alpha if Item Deleted
GMPuse	709
DesignDocProv	746
GAMPuse	715
ValDesignedIn	756
ValDocAvail	701
RegCompAuditsProd	786
SourceCodeAvail	743
ERES	731

Reliability Statistics

Cronbach's Alpha	N of Items
763	8

Table 3 5 7 4 Scale reliability for Regulatory items

	Cronbach's Alpha if Item Deleted
ProfitLevelchange5yrPharma	790
SalesVolChange5yrPharma	728
NewProdSalesPharma2yr	688
MarketShareRelative	729
Competitiveness	686

Reliability Statistics

Cronbach's Alpha	N of Items
766	5

Figures 3 5 7 1 to 3 5 7 3 show the distributions of sub-variable scores for the pilot data and the corresponding main variable score distributions

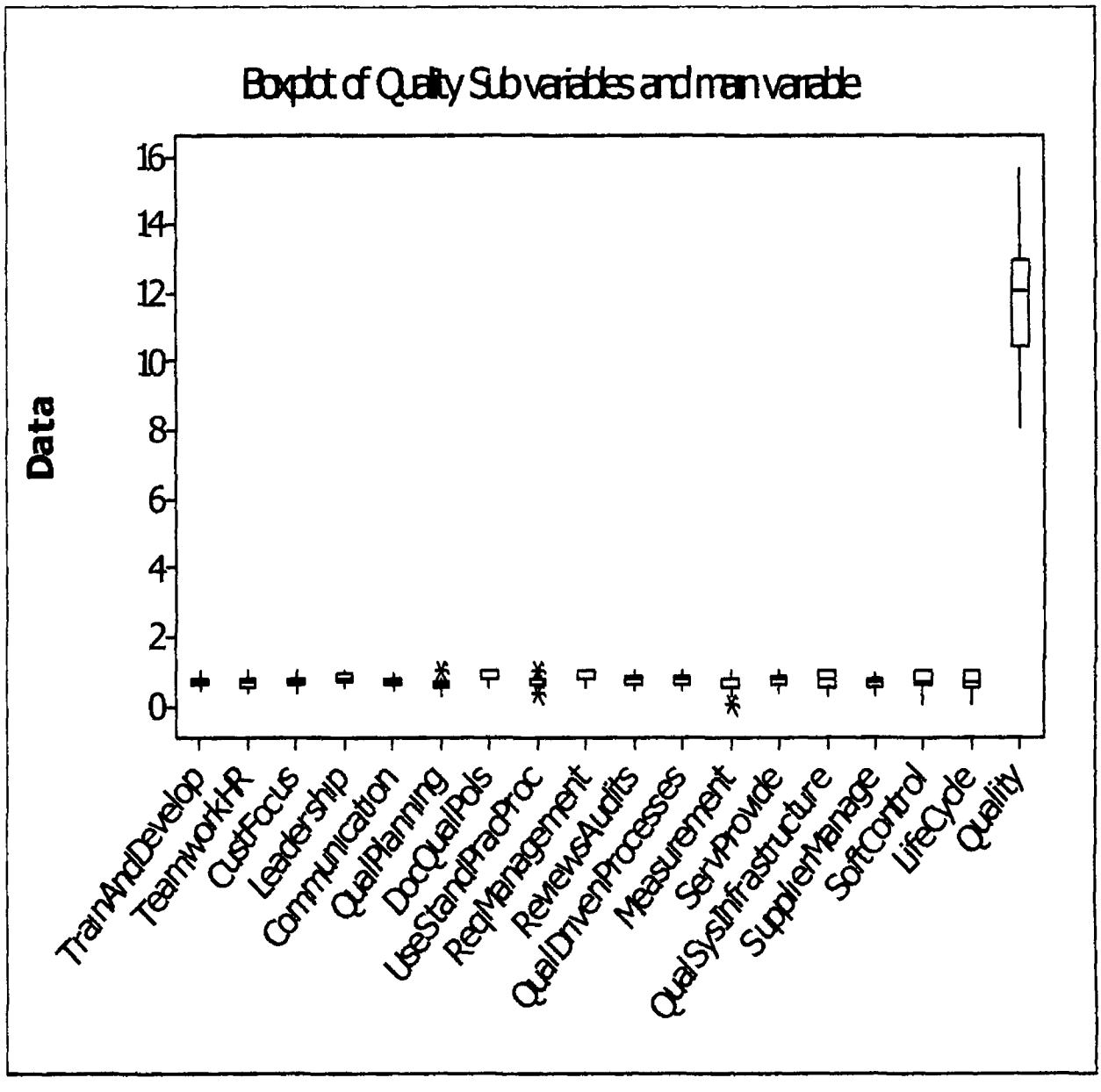


Figure 3 5 7 1 Boxplot showing scaled range of sub-variable scores and corresponding summated main variable for Quality

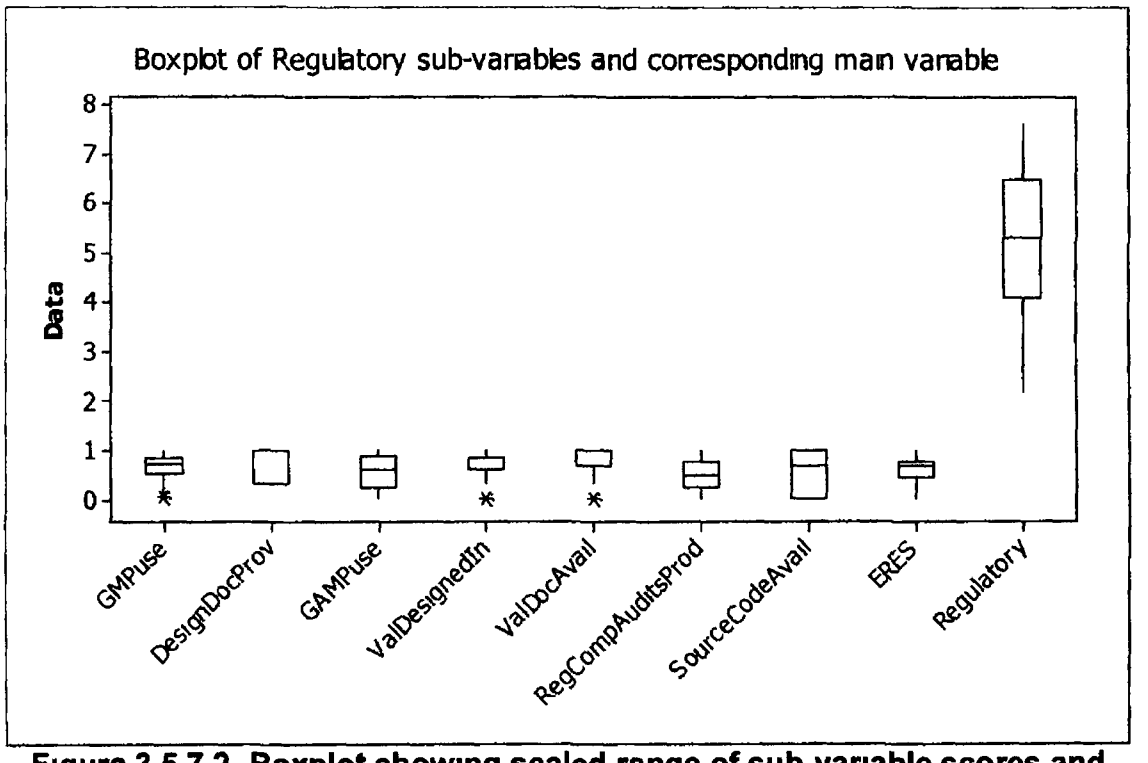


Figure 3 5 7 2 Boxplot showing scaled range of sub-variable scores and corresponding summated main variable for Regulatory

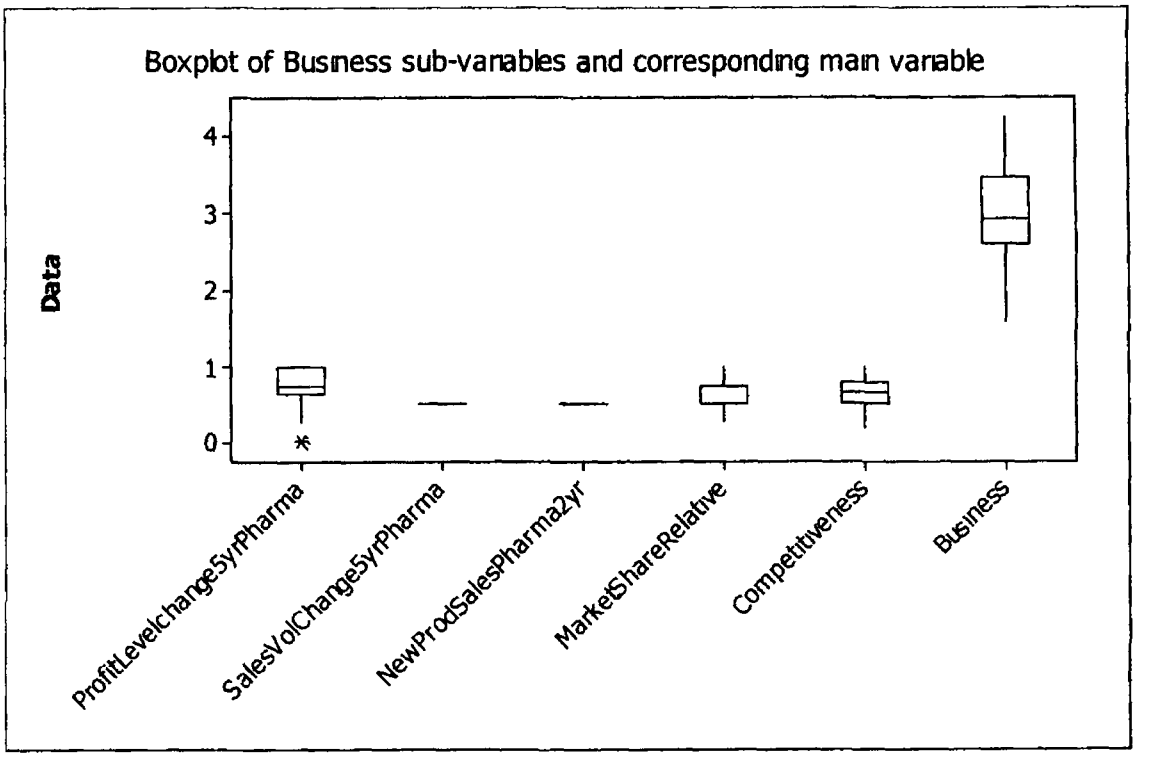


Figure 3 5 7 3· Boxplot showing scaled range of sub-variable scores and corresponding summated main variable for Business.

As described below, correlation analysis was then used to determine the nature of the core relationships and study hypotheses Some non-parametric difference testing was carried out using the background variables to test for potential bias, and to check to see whether the correlation findings would be valid across a range of scenarios Partial correlation was used to check for spuriousness, intervening and moderating variables and where significant important relationships were found, regression was carried out to present predictors

3 5 8 Describing the pilot data

For N=29, 82% of responses were from companies who were established more than 16 years, i e well established Only 1 respondent had been in business for less than 8 years 65 5% of respondents had been operating in the pharmaceutical market for more than 16 years, with 17% operating in that market for less than 8 years These percentages might mean some non-response bias might be present in the main study in terms of non-responses from companies not well established or not well established in providing for pharmaceutical manufacturers at least

A good spread of company sizes was represented (Table 3 5 8 1) with 200 employees being the cut off point for 'large' companies

Table 3 5 8 1 Organization size distribution

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0-50	7	24 1	24 1	24 1
	51-100	6	20 7	20 7	44 8
	101 150	3	10 3	10 3	55 2
	151-200	5	17 2	17 2	72 4
	>200	8	27 6	27 6	100 0
	Total	29	100 0	100 0	

Similarly, reasonably flat distributions for product criticality and automation complexity were evident from the pilot data (Tables 3 5 8 2 and 3 5 8 3)

Table 3 5 8 2 Criticality of products to end product quality

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	0	1	3 4	3 4	3 4
	1	1	3 4	3 4	6 9
	2	4	13 8	13 8	20 7
	3	6	20 7	20 7	41 4
	4	1	3 4	3 4	44 8
	5	7	24 1	24 1	69 0
	6	9	31 0	31 0	100 0
	Total	29	100 0	100 0	

(Where a score of 6 represents the highest criticality)

Table 3 5 8 3 Complexity of automation used in products

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1	1	3 4	3 4	3 4
	2	2	6 9	6 9	10 3
	3	8	27 6	27 6	37 9
	4	4	13 8	13 8	51 7
	5	3	10 3	10 3	62 1
	6	11	37 9	37 9	100 0
	Total	29	100 0	100 0	

(Where a score of 6 represents the highest criticality)

This indicated that sufficient cases would exist in the main study from across the range of possible product criticality and automation complexity determinations by respondents to ensure that any analysis was relevant across the range That is, there were enough responses in the low (1&2), medium (3&4), and high (5&6) ranges to carry out a meaningful analysis Hence bias would be unlikely due to sufficient representation from companies who produce low complexity automation in

their products and whose products have little impact on product quality Correlations (section 3 5 8 1) would determine any impact on the study variables due to complexity and criticality

In order for the study to be externally valid across the range of possible regulatory environments it was important to see how the data differed throughout the regulatory combinations exhibited by respondents It was possible for companies to work within any combination of regulatory environments That is, they could work within none (or unknown), one regulatory environment, or many Scores were compared for the three main study variables for each regulatory environment and where the environment was unknown (Table 3 5 8 4) A non-parametric Mann-Whitney *U*-test was carried out to see whether the differences between scores were statistically significant for absence or presence of a given environment Non-parametric tests are also more powerful than parametric tests where sample sizes are low [167]

Table 3 5 8 4 Differences in median scores for 3 main study variables for presence and absence of admission of regulatory environment (using Mann Whitney-U)

EMEA	Qual	FDA	Qual	ICH	Qual	PIC/S	Qual	WHO	Qual	Unknown	Qual
Yes	13 0	Yes	11 8	Yes	12 5	Yes	12 5	Yes	12 8	Yes	13 1
No	11 7	No	13 1	No	12 2	No	12 2	No	12 0	No	11 8
Sig	067	Sig	217	Sig	758	Sig	453	Sig	521	Sig	217
	Reg*		Reg		Reg		Reg		Reg*		Reg
Yes	6 1	Yes	5 1	Yes	6 1	Yes	6 1	Yes	6 2	Yes	3 4
No	4 8	No	3 4	No	5 0	No	4 8	No	4 8	No	5 1
Sig	043	Sig	101	Sig	107	Sig	254	Sig	042	Sig	101
	Bus		Bus		Bus		Bus		Bus		Bus
Yes	3 3	Yes	2 9	Yes	3 0	Yes	2 3	Yes	2 5	Yes	3 1
No	2 9	No	3 1	No	2 9	No	3 0	No	3 0	No	2 9
Sig	237	Sig	754	Sig	245	Sig	845	Sig	181	Sig	784

* Significant at the p= 05 level (2-tailed)

In Table 3 5 8 4 there were few statistically significant differences between scores at the pilot test stage, however differences in median scores were evident as expected Where the main regulatory environments (EMEA, FDA and PICs) were confirmed from questionnaires, median regulatory scores were always higher In the case of the EMEA this was significant at the p= 05 level As the hypothesis for whether the scores would be greater or less was not specified it was non-directional and hence two-tailed levels of significance were invoked There was a less clear distinction between quality and business scores across the range of regulatory environments

To compare scores between the various regulatory combinations a Kruskal Wallis test for N-independent samples (non-parametric) was performed using the regulatory variable as dependent No statistically significant difference was found between groups as p=0 145 (Table 3 5 8 5)

Table 3 5 8 5 Results of Kruskal Wallis test for significant differences in regulatory scores between regulatory groupings

Ranks

	REGCOMP	N	Mean Rank
Regulatory	FDA Only	11	14 00
	EMEA and FDA	5	16 40
	FDA + PICs	2	13 00
	EMEA + FDA + PICs	3	24 50
	Unknown	7	10 07
	Total	28	

	Regulatory
Chi Square	6 840
df	4
Asymp Sig	145

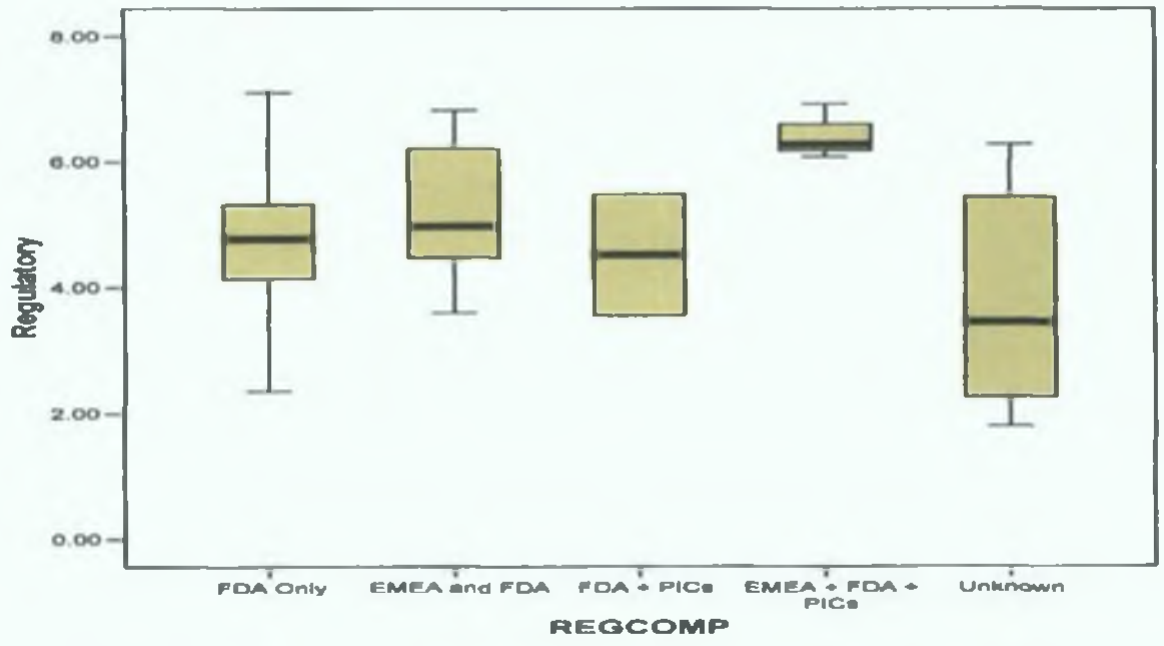


Figure 3.5.8.1 Box-plots for various regulatory combinations with the dependent regulatory variable (pilot).

Although not significant with N=28, the box-plots in figure 3.5.8.1 show that the median scores differed. Where the EMEA were involved, median scores tended to be higher; however considerable overlap existed across the ranges for 'FDA only', 'EMEA and FDA', and FDA and PIC/S. Where all three primary regulatory environments were involved together, a higher median score and range were evident. As expected, where the regulatory environment was unknown by respondents, the median score was lower than where it was known. However the upper range of the 'unknown' box-plot overlapped with the cases where regulatory environments were known. This suggested that it was possible to have a comparable regulatory score while not knowing what regulatory environment the company was producing for. In general though from the pilot data, no significant

differences existed between regulatory scores and regulatory environment so that any findings could not be generalized across the regulatory range

Of the 29 pilot study respondents, 20 reported to be ISO 9001 registered There were a very low number of pilot respondents who reported using the other options (CMM, Six Sigma and TQM) A Mann-Whitney-U test was carried out to compare the non-parametric differences between two groups, those with and without ISO quality management systems A significant difference was found in quality scores, however no difference existed over the regulatory and business variables for presence or absence of an ISO QMS This correlation confirmed what was found elsewhere in the literature [92][94][96][97] Table 3 5 8 6 and the box-plot in figure 3 5 8 2 show the differences between scores for companies with and without ISO registration

Table 3 5 8 6 Mann Whitney-U test for differences between main study variables for companies with and without ISO 9000 9001 quality management systems

	Quality	Regulatory	Business
Mann-Whitney U	45 500	61 000	85 000
Wilcoxon W	90 500	97 000	295 000
Z	-2 098	967	- 236
Asymp Sig (2-tailed)	036	334	813
Exact Sig [2*(1-tailed Sig)]	034(a)	354(a)	835(a)

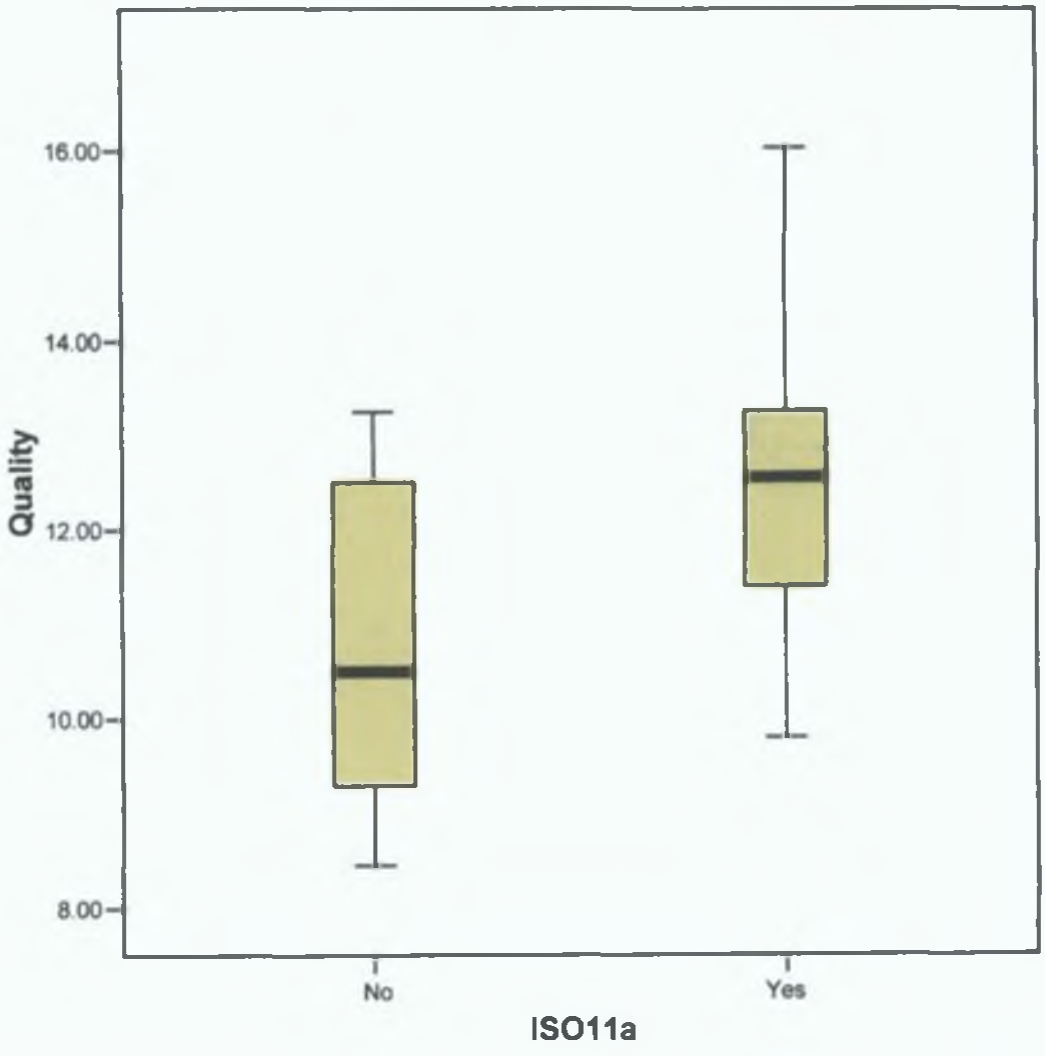


Figure 3.5.8.2: Box-plot for Quality scores for companies with and without ISO registration.

3.5.8.1 Correlation analysis

Parametric and non-parametric correlation analyses were carried out between the main study variables, between all the sub variables and between the main study variables and the sub variables. Low and moderate correlations were evident in

some important areas although statistical significance was not always evident, in many cases this was possibly due to the small sample size

Kendall's tau-b was used as the main correlation test Very similar results were achieved using the parametric Pearson's-r test and the non-parametric Spearman's rho in terms of strength and direction of correlations and statistical significance As no direction of relationships was hypothesized for the tests, 2-tailed levels of significance were employed Table 3 5 8 1 1 shows Kendall's tau-b evaluated for the main study variables

Table 3 5 8 1 1 Kendall's tau-b evaluated for the main study variables

Correlations

			Quality	Regulatory	Business
Kendall's tau_b	Quality	Correlation Coefficient	1 000	281(*)	229
		Sig (2-tailed)		036	084
		N	29	28	29
	Regulatory	Correlation Coefficient	281(*)	1 000	- 075
		Sig (2-tailed)	036		579
		N	28	28	28
	Business	Correlation Coefficient	229	- 075	1 000
		Sig (2-tailed)	084	579	
		N	29	28	29

* Correlation is significant at the 0 05 level (2-tailed)

There was a low positive correlation between Quality and Regulatory scores This was significant at the p=0 05 level There was also a low positive relationship between Quality and Business scores, however this was not significant (p= 084) at the pilot stage The most striking finding was that there was no direct correlation between the Regulatory variable and the Business variable This confirmed the null

hypothesis H3o (i e H3 was rejected at this point, albeit only in the pilot study) However it was possible to conclude that quality systems might be *driven* by regulatory requirements (as is evident in part from the data) and that regulatory factors directly impact business performance Figure 3 5 8 1 1 gives an overview of the pilot correlations

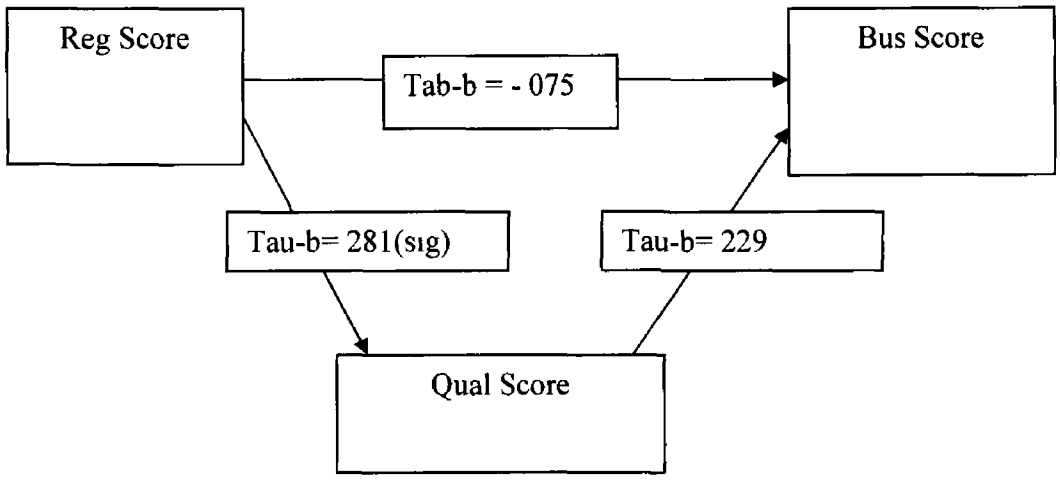


Figure 3 5 8 1 1 Relationships between main study variables after pilot testing (Kendall's tau-b)

It should be noted however that the quality score was not significantly correlated to the business scores for the pilot data, however it was not far from being significant, so from an exploratory perspective, the correlation could not be ignored This relationship would become clearer when the main study data was analyzed A simple linear regression analysis yielded an un-standardized regression equation of

EQ1 Quality = 9 819 + 457 Regulatory

Constant standard error = 1 07

Coefficient standard error = 0 214

2-tailed significance = 043

Although the errors were potentially large, this did show that regulatory scores could be used as a statistically significant predictor of Quality As Quality was not, at this point, significantly correlated to business scores, this regression analysis was not given much credence as errors were too large to allow reasonable prediction and the regression was not itself significant

Other useful significant correlations were evident from the sub-variable analyses (at the p= 05, two-tailed level) A low positive correlation was found between the time the company was established in the pharmaceutical market and the quality system infrastructure score (tau-b = 0 334, N=29) This gave further weight to the possibility that regulatory influence may be a cause in part of quality system performance

Organisation size correlated significantly with automation complexity used in products (tau-b = 0 368) This suggested that complex automation is related to organisation size Importantly, organisation size was not correlated with business performance, regulatory performance or business performance scores This meant that findings would be equally valid across the range of company sizes This was later confirmed using partial correlation Complexity was also correlated positively

and significantly with the software control variable (tau-b = 347) and to whether regulatory audits are carried out (tau-b = 0 340) That is, software complexity was related to software control (a sub-variable of Quality) and to the extent to which regulatory audits take place This was consistent with the requirements of GAMP [13] and other software development guidelines [41][42][122] where efforts should be matched to risk, which increases with complexity Additional complexity might also suggest additional functionality, which would leave the software open to the requirements of 21 CFR Part 11 and other regulations pertaining to software This could explain the pilot study relationship between complexity and the extent which regulatory audits are carried out

The criticality of end product to end product quality was significantly correlated with a number of other variables Notably these were the regulatory variable (tau-b = 0 418) and with the sub-variables 'GMP use' (tau-b = 0 387), and 'Provision of Design Documentation' (tau-b=0 381) and use of GAMP (0 339)

Another significant pilot data correlation (background variables) was between the percentage revenue companies acquired from the pharmaceutical market and perceived competitiveness in that market (tau-b = 0 353) That is, there seemed to be a positive relationship between those companies who relied mostly on the pharmaceutical market and their competitiveness

For the main study variables, a partial correlation test was carried out controlling the background variables (Criticality, Complexity, Org size, Established time, Established Time in Pharma) Pearson's r was used in this test as the correlation indicator As the Kendall's tau-b zero order correlations were very close to the Pearson's r values, any diminished correlation due to spuriousness, moderating or intervening variables would be evident from this parametric test and useful

Table 3 5 8 1 2 Partial correlations of all background variables controlled, the main study variable relationships compared against zero order correlations

Control Variables			Regulatory	Business	Quality
-none-(a)	Regulatory	Correlation	1 000	- 003	386
		Significance (2-tailed)		989	043
		df	0	26	26
	Business	Correlation	- 003	1 000	321
		Significance (2-tailed)	989		096
		df	26	0	26
	Quality	Correlation	386	321	1 000
		Significance (2-tailed)	043	096	
		df	26	26	0
Est1 & PharmEst2 & OrgSize3 & Complexity4 & Criticality8	Regulatory	Correlation	1 000	121	339
		Significance (2-tailed)		584	113
		df	0	21	21
	Business	Correlation	- 121	1 000	300
		Significance (2-tailed)	584		164
		df	21	0	21
	Quality	Correlation	339	300	1 000
		Significance (2-tailed)	113	164	
		df	21	21	0

a Cells contain zero-order (Pearson) correlations

It can be seen from Table 3 5 8 1 2 that the magnitude of the correlation between Quality and Regulatory was not much reduced (0 386 to 0 339) and is certainly not eliminated So it would hold that there still remained a direct relationship between

Quality and Regulatory scores and the relationship is not spurious Similarly, the correlation between Quality and Business held despite the controlling of the background variables The statistical significance for both of these relationships did suffer however, it was believed mainly due to the low sample size The Quality variable was correlated with Market share (tau-b = 0 320) and Perceived Competitiveness (tau-b = 0 285), which were sub-variables of the Business variable This again confirmed what the literature indicated

Interestingly the 'GMP use' variable was significantly and positively correlated with many of the Quality sub-variables These included Training and Development (tau-b = 0 486), Teamwork and HR (tau-b = 0 305), Quality Planning (tau-b = 0 354), Use of Standards Practices and Procedures (tau-b = 0 373), Reviews and Audits (tau-b = 0 289), Quality Driven Documented Processes (tau-b = 0 314), Supplier Management (tau-b = 0 367), Software Control (tau-b = 0 356), Life Cycle use (tau-b = 0 325), and the summated main Quality variable (tau-b = 0 436) These correlations were not unexpected as the fundamentals of GMP are to do with people, quality systems, reviews and audits, documentation and record keeping and software control Many of the quality sub-variables are in fact explicitly detailed as requirements in the GMPs [59][70]

Another interesting correlation was that between the ERES variable and software control and life cycle use variables (tau-b = 0 454 and 0 458 respectively) As compliance with the ERES requirements [23][37] requires software control at

development stages, and use of life cycle development is conducive to that control and development quality, this was an important and expected correlation

3 6 Summary of Pilot study

The main findings of the pilot study were that the regulatory practices and quality practices were correlated and that there is evidence that regulatory practices tend to correlate with quality practices Quality practices were correlated with competitiveness and market share within the pharmaceutical industry, although not significantly correlated with business practices for N=29 Hence H1 would be accepted tentatively There was also a positive and significant correlation between quality and regulatory practices, meaning that H2 could be accepted for the pilot study There was no correlation between regulatory practices and business practices and hence H3 could be rejected with confidence (based on the pilot study)

Chapter 4: Primary study

The questionnaire was sent to all those potential respondents who had not been represented in the pilot study From the sampling population of 647, 219 agreed to participate (33 8%) Of the 219 who agreed, 122 or 55 7% responded, including the 29 pilot study respondents This meant a total response rate of 18 9% and exceeded the target of 100 completed questionnaires Three questionnaires were unusable because entire sections were incomplete This response rate was considerably higher than that typically expected using e-mail surveys [147][148] but lower than the 70 7% response achieved for the pilot study, although the administration procedure used in the pilot study was used in full This lower response rate was possibly due, at least in part, to summer administration of the main study Many of the initial e-mails for the main study were sent out during the traditional vacation months of July and August and there was a noticeable increase in 'out-of-office' responses during those months Follow ups after the holiday period were carried out as per the normal administration procedure, but the response rate although steady, did not approach that experienced for the pilot study The rate was however more than sufficient for the purposes of this research

Although there was a low rate of missing items, 21 questionnaires had at least one missing answer Questionnaire item 9 which asked about the type of organisation the respondent worked in (in terms of whether it worked within the customer's sites or external from them) was frequently misinterpreted or misunderstood This

question was deemed unreliable and hence would not be used for any analytical purposes Similarly the open question on 'use of standards' was generally not answered, it provided no useful information

In total 59 items were missing across 119 questionnaires each with 84 questions giving a missing rate of 0 59% The distribution of missing answers was evenly spread across 38 questionnaire items, so there were no patterns, which might lead to concerns over bias

Of the 122 received, 79 (64 8%) were submitted through the use of the web-survey form, 3 (2 5%) were submitted by post and 40 (32 8%) were submitted using the MS Word™ document as an attachment All questionnaires were printed when received The data was input directly into SPSS manually and a data comparison was carried out between the data downloaded from the web-survey site and the manual data No discrepancies were found, thus validating the manual process

4 1 Analysis of main study data

The analytical strategy for the main study was derived mainly from the pilot study strategy The larger N for the main study meant that additional tools such as factor analysis could be employed A sample size of greater than 100 is generally found to be appropriate for such analysis [167] The use of summated scales based on factor analysis output meant that small intervals existed within the factor scores meaning that it would be appropriate to use parametric as well as non-parametric testing [167] In general, because there is some controversy in the use of parametric techniques in this type of setting [166][167], non-parametric analyses were performed where possible as a check on the results from parametric tests

The strategy was

1 Present and analyse descriptive statistics and data distributions
    - 1 1 Organisation size distributions
    - 1 2 Time in business distributions
    - 1 3 Regulatory environment distributions
    - 1 4 Quality environment distributions
    - 1 5 Complexity of automated element distributions
    - 1 6 Criticality to user end-product quality distributions
2 Factor Analysis to find underlying dimensions in data related to main study variables
    - 2 1 Exploratory factor analysis
    - 2 2 Principal components analysis

2 3 Derivation of factors

2 3 1 Retention of components

2 3 2 Elimination of items

2 3 3 Resulting factors

2 3 4 Reliability analysis of summated scales

2 3 5 Distribution of summated scale for study data

3 Main explorations and hypothesis testing

3 1 Factor correlations

3 2 Factor regression

3 3 Relationships between background variables and factors

3 3 1 Categorical differences

Figure 4 1 1 illustrates the overall data processing strategy

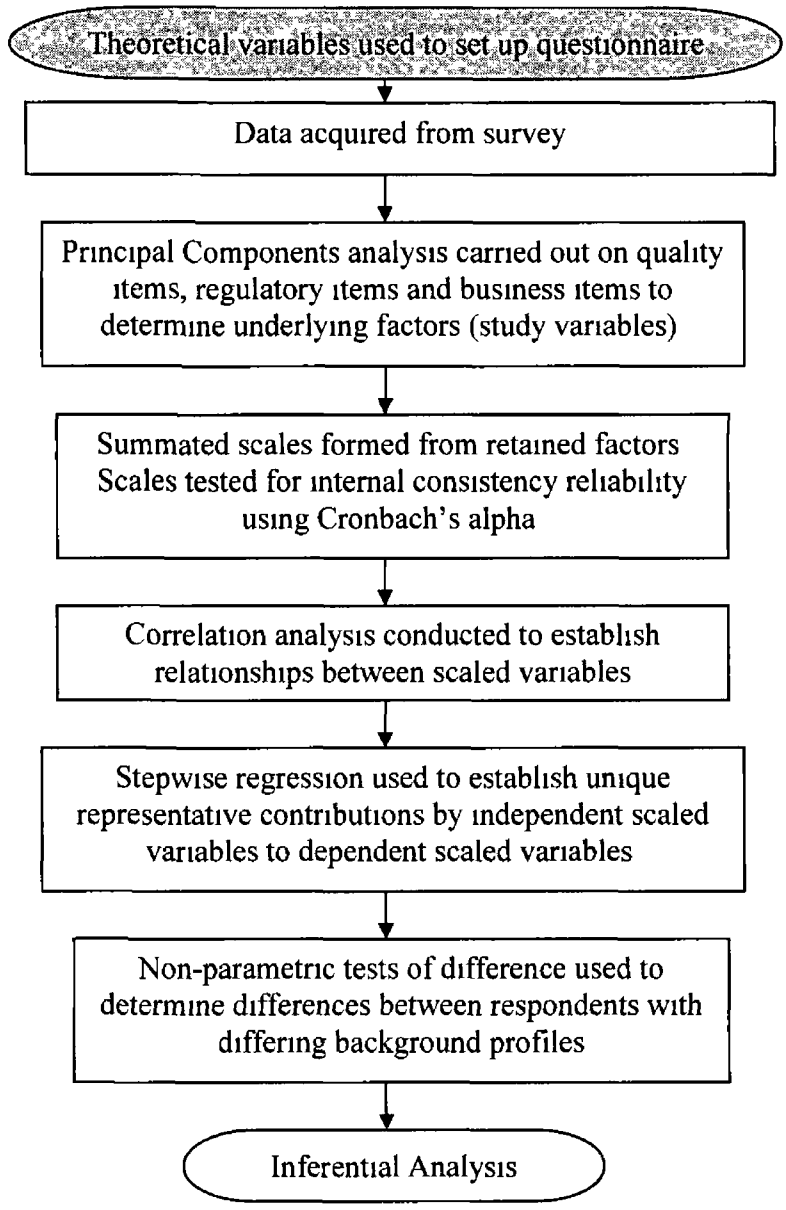


Figure 4 1 1 Process flow diagram for data analysis phase

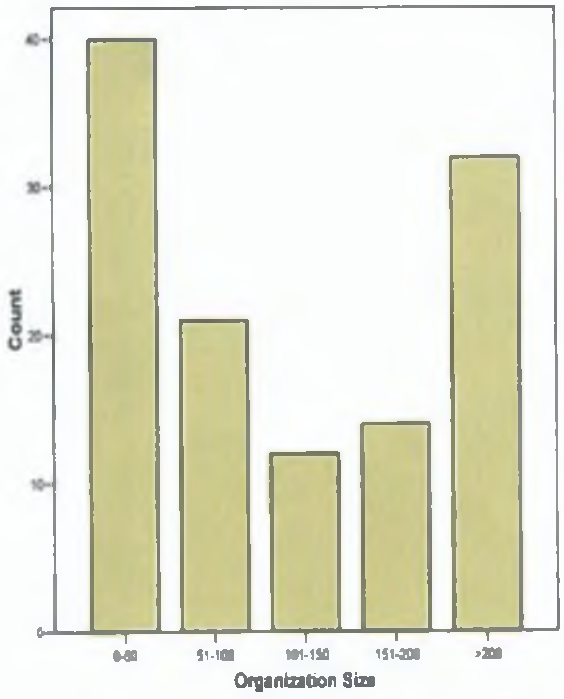
4 2 Descriptive statistics and distributions

It was important that the distribution of data was obtained from across the spectrum of company sizes, length of time in business and operating in the pharmaceutical market and also across the regulatory environment and quality system environment Other important background considerations, which might theoretically contribute to variance in the data, were the criticality of the respondent's product to the quality of the customer's end product and the complexity of the automation used in the respondent's end product These 6 aspects made up the main background variables for the study The distributions needed to be assessed to ensure that no bias could be present in the data due to absence of information from particular sectors Once valid factors were developed for the data, categorical analysis was then conducted to evaluate cross-categorical differences using the background variables It was not expected that the background variables would show normal distributions and hence care had to be taken when carrying out analyses to ensure that appropriate tests were applied

It was important for many of the background variable distributions to show responses from across the range of possible options This was necessary to show that the study was representative across those ranges, to rule out possible non-response bias, and to allow evaluation of the results across sub-groups within the ranges For all the background variables, acceptable distributions were found

4.2.1 Organization size distribution

From the 119 valid questionnaires, there was an acceptable representation from across the range of possible company sizes as represented in figure 4.2.1.1.



		Frequency	Valid Percent
OrgSize	0-50	40	33.6
	51-100	21	17.6
	101-150	12	10.1
	151-200	14	11.8
	>200	32	26.9
	Total	119	100.0

Figure 4.2.1.1 Organization size distribution.

Forty small companies were represented and 32 large companies with 47 mid size companies making up the remainder as can be seen in figure 4.2.1.2 below.

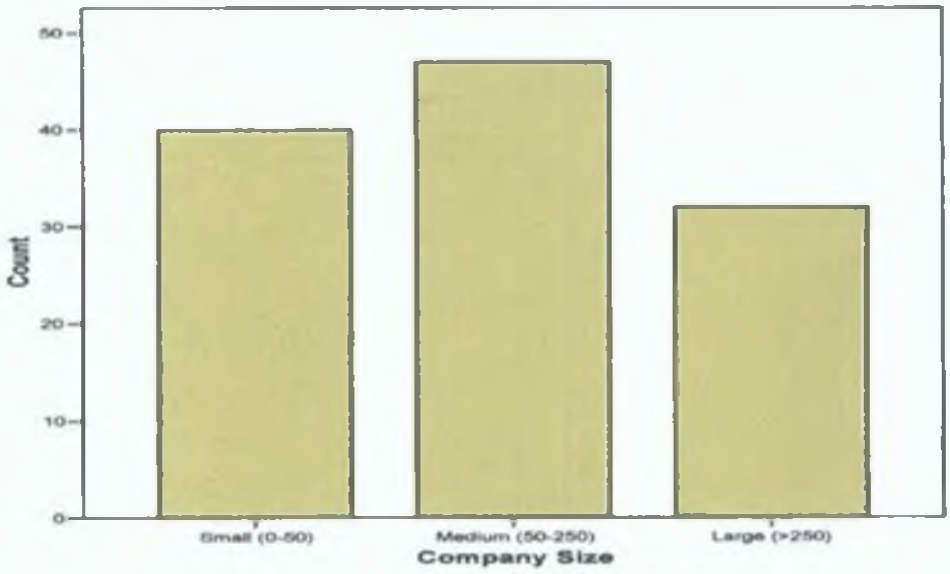
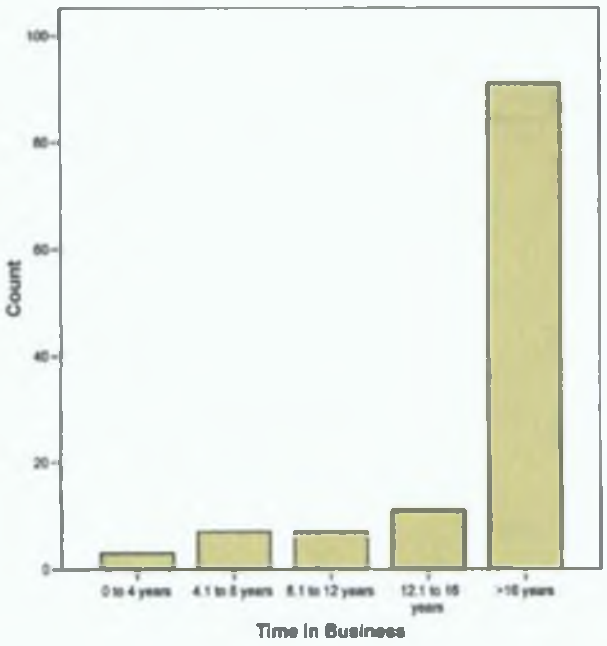


Figure 4.2.1.2 Summary of company size distribution.

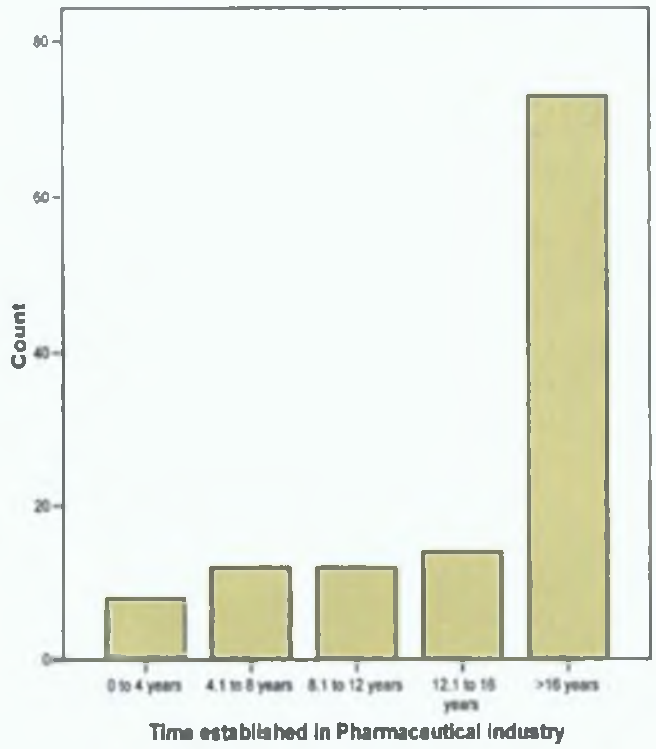
4.2.2 Length of time in business distributions

This background variable was divided into two categories, length of time in business and length of time operating in the pharmaceutical business. Cases were present for the entire range of possibilities as can be seen in figures 4.2.2.1 and 4.2.2.2. It is clear that the majority (61.3%) of respondents were established in the pharmaceutical market for over 16 years. Overall, 76.5% of the respondents had been in business for more than 16 years. Sufficient data existed for all those other categories of length of time in business and length of time in the pharmaceutical industry to carry out comparative analysis of companies established more and less than 16 years. Figures 4.2.2.3 and 4.2.2.4 show the summarized frequencies for these categories.



		Frequency	Percent
Time in Business	0 to 4 years	3	2.5
	4.1 to 8 years	7	5.9
	8.1 to 12 years	7	5.9
	12.1 to 16 years	11	9.2
	>16 years	91	76.5
	Total	119	100.0

Figure 4.2.2.1 Length of time in business distribution.



		Frequency	Percent
Time in Pharma	0 to 4 years	8	6.7
	4.1 to 8 years	12	10.1
	8.1 to 12 years	12	10.1
	12.1 to 16 years	14	11.8
	>16 years	73	61.3
	Total	119	100.0

Figure 4.2.2.2 Length of time in pharmaceutical industry distribution.

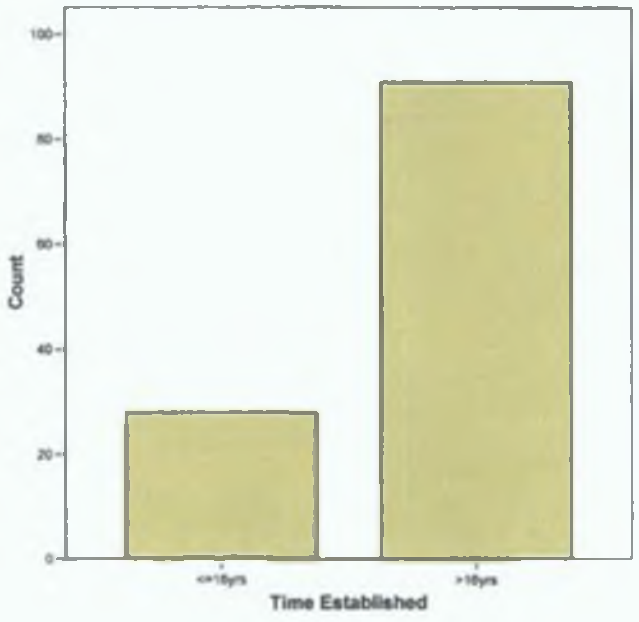


Figure 4.2.2.3 Length of time in business summarized frequencies.

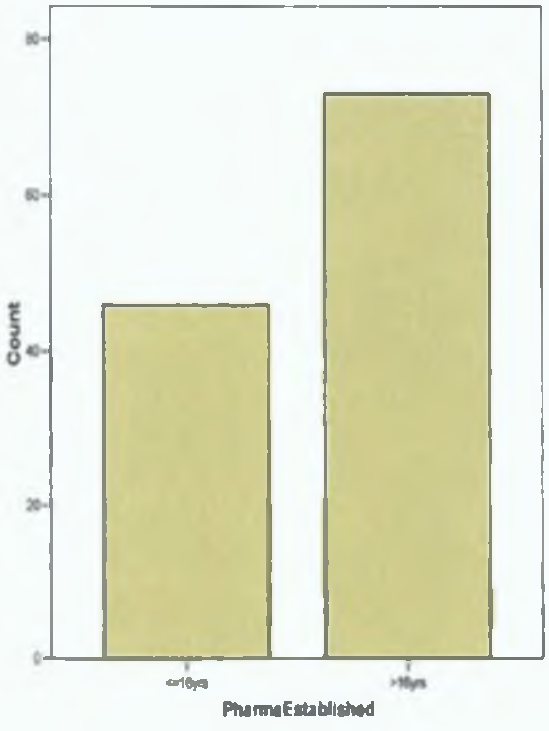


Figure 4.2.2.4 Length of time in pharmaceutical market summarized frequencies.

4 2 3 Regulatory distribution

Of the five possible categories of regulatory environments 9 different permutations emerged from the study as can be seen below in figure 4 2 3 1 and table 4 2 3 1 There were 60 of the 118 respondents who produced for FDA regulated environments only Only 2 respondents developed systems solely for the EMEA market only with 26 others developing for both the EMEA and FDA markets (combined with some others such as the PIC/S and the ICH guidelines) The data was summarised into three groups to ease understanding and analysis, as can be seen in the bar chart in Figure 4 2 3 2 Here the regulatory environment was divided into 'FDA only', FDA and others' and 'Unknown' 26 respondents reported that they did not know their regulatory environments From this it can be seen that those who produced for the EMEA market generally produced for the FDA market, but the converse is not true

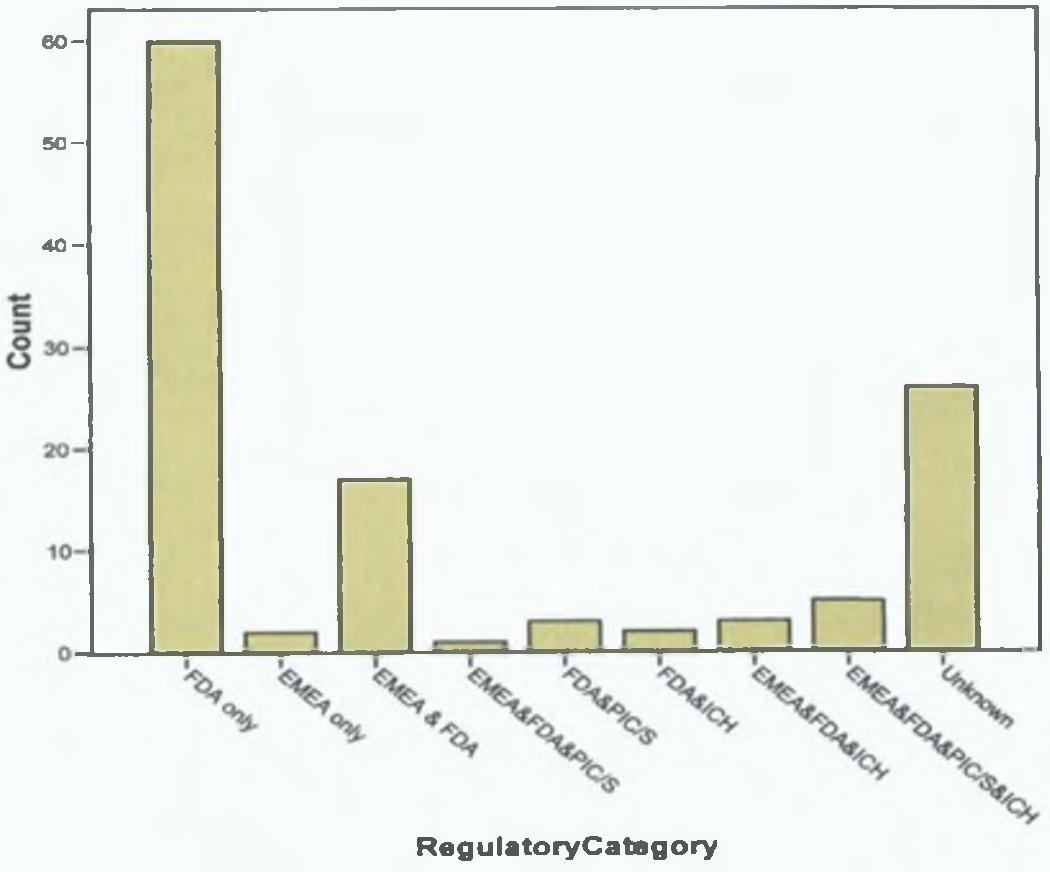
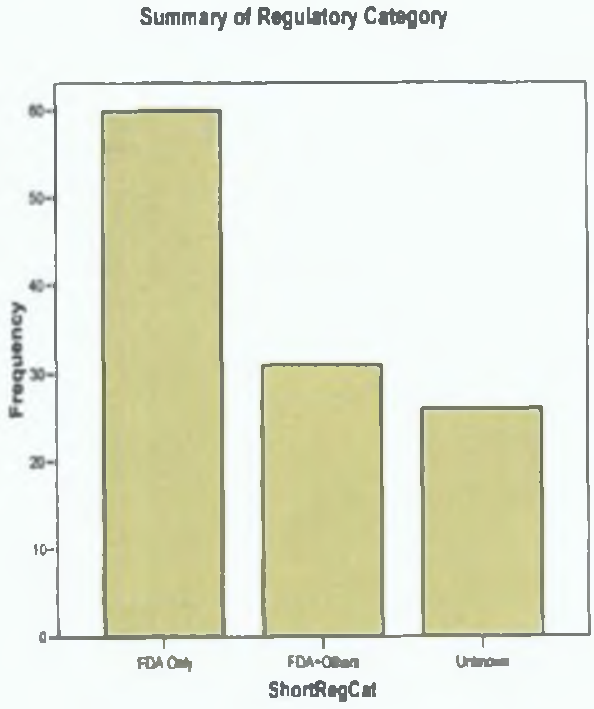


Figure 4.2.3.1 Regulatory environments of respondents.

Table 4.2.3.1 Regulatory environments of respondents.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	FDA only	60	50.4	50.4	50.4
	EMEA only	2	1.7	1.7	52.1
	EMEA & FDA	17	14.3	14.3	66.4
	EMEA&FDA&PIC/S	1	.8	.8	67.2
	FDA&PIC/S	3	2.5	2.5	69.7
	FDA&ICH	2	1.7	1.7	71.4
	EMEA&FDA&ICH	3	2.5	2.5	73.9
	EMEA&FDA&PIC/S&ICH	5	4.2	4.2	78.2
	Unknown	26	21.8	21.8	100.0
	Total	119	100.0	100.0	

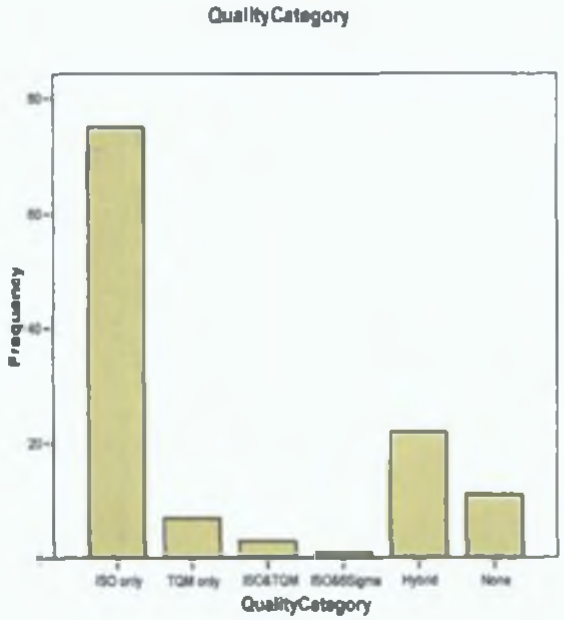


		Frequency	Percent
Valid	FDA Only	60	50.4
	FDA+Others	31	26.1
	Unknown	26	21.8
	Total	117	98.3
Missing	System	2	1.7
Total		119	100.0

Figure 4.2.3.2 Length of time in pharmaceutical industry distribution.

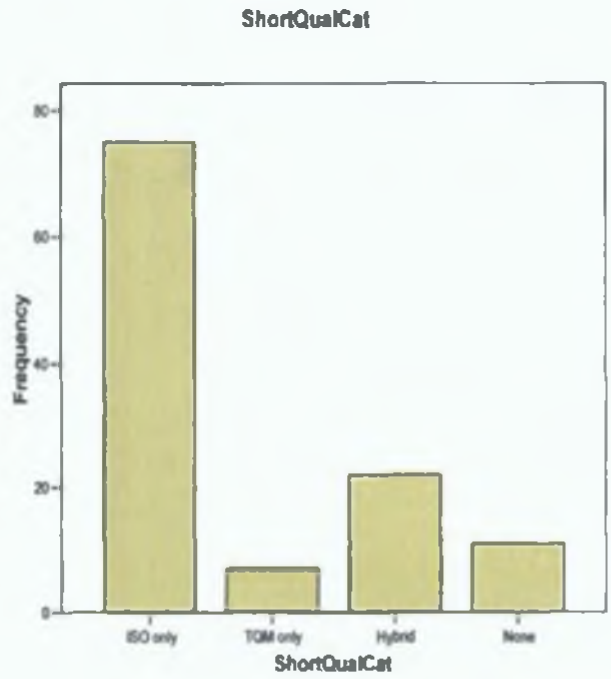
4.2.4 Quality Management system distribution

The distributions for quality system management environment as specified in the questionnaire are shown in figure 4.2.4.1. The data was then summarised into four categories (ISO only, TQM only, Hybrid and No QMS environments), which represented 96.7% of the cases in the data. Figure 4.2.4.2 shows the distribution for the summarised quality categories.



		Frequency	Percent
Valid	ISO only	75	63.0
	TQM only	7	5.9
	ISO&TQM	3	2.5
	ISO&6Sigma	1	.8
	Hybrid	22	18.5
	None	11	9.2
	Total	119	100.0

Figure 4.2.4.1 Quality System Environment distribution.

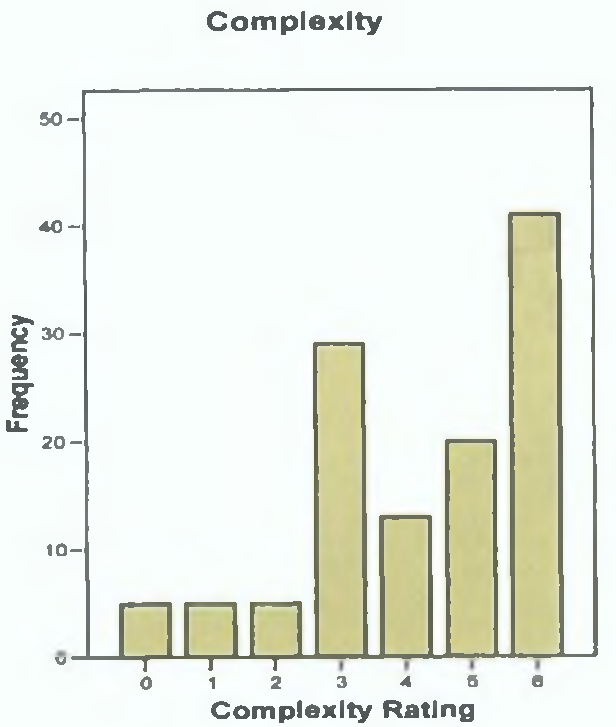


		Frequency	Percent
Valid	ISO only	75	63.0
	TQM only	7	5.9
	Hybrid	22	18.5
	None	11	9.2
	Total	115	96.6
Missing	System	4	3.4
Total		119	100.0

Figure 4.2.4.2 Quality System Environment summarised categories distribution.

The array of environments present in the data meant that analysis could be performed across the subgroups to test for differences and for comparison with the literature.

4.2.5 Complexity of automation in end production distribution

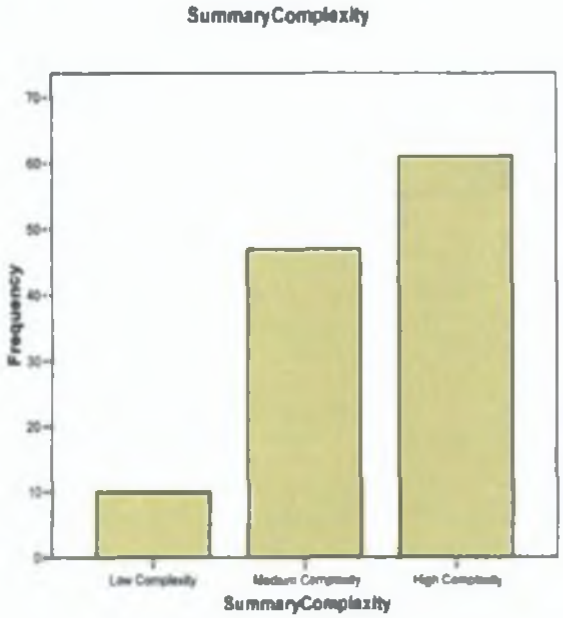


		Frequency	Percent
Valid	0	5	4.2
	1	5	4.2
	2	5	4.2
	3	29	24.4
	4	13	10.9
	5	20	16.8
	6	41	34.5
	Total	118	99.2
Missing		1	.8
Total		119	100.0

Figure 4.2.5.1 Automation complexity distribution.

As can be seen in figure 4.2.5.1, there was a good spread of respondents from those who rated the complexity of the automation making up their products as low, to those who rated theirs as high. This was an important background variable and

sufficient representation was necessary from across the range of complexities. The data could be further summarised into low-medium-high categories by considering 0-1 as low complexity, 2-4 as medium complexity and 5-6 as high complexity (although it could be argued that the data could be handled ordinally also, as was done later in the analysis for completeness). Figure 4.2.5.2 below shows the summarised complexity frequencies.



		Frequency	Percent
Valid	Low Complexity	10	8.4
	Medium Complexity	47	39.5
	High Complexity	61	51.3
	Total	118	99.2
Missing		1	.8
Total		119	100.0

Figure 4.2.5.2 Summary of automation complexity distribution.

4.2.6 Criticality distribution

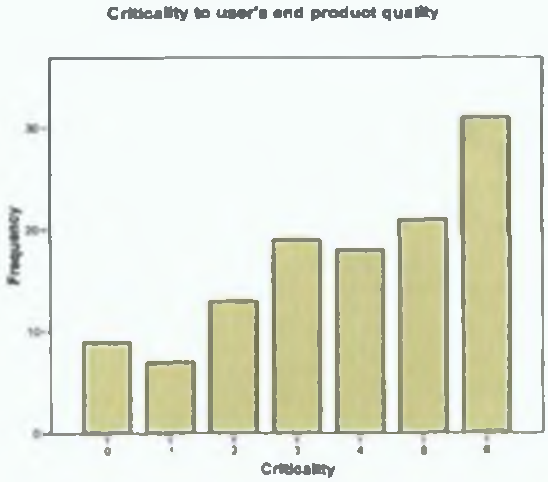
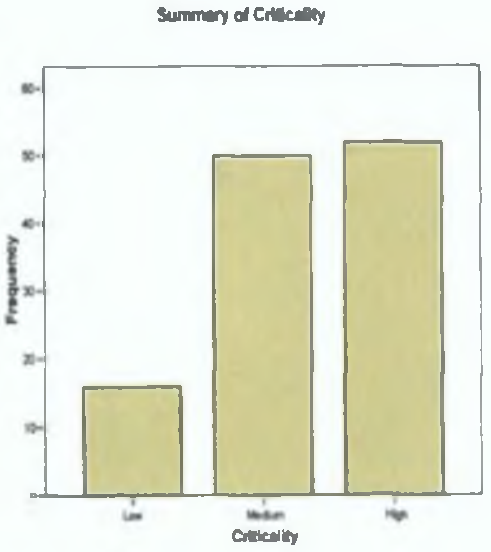


Figure 4.2.6.1 Criticality to end user product quality distribution.

Figure 4.2.6.1 above shows the distribution of how critical the respondent's believed their systems to be to the end user's product quality. Again, a good distribution across the range of possible criticality levels was obtained to allow analysis across the range for differences in dependent scores. Figure 4.2.6.2 below summarises these criticality ratings in terms of low (0-1), medium (2-4) and high (5-6) criticalities to allow categorical analysis and ease of understanding of the distribution and its effects.



		Frequency	Percent
Valid	Low	16	13.4
	Medium	50	42.0
	High	52	43.7
	Total	118	99.2
Missing		1	.8
Total		119	100.0

Figure 4.2.6.2 Summary of criticality to end user product quality distribution.

4.3 Exploratory Factor Analysis

In the development stages of the study a set of constructs were derived from the literature that attempted to represent a set of sub-variables, each sub-variable in turn then being used as an indicator for Quality Practices, Regulatory Practices and Business Performance 'parent' variables. The relationships between the sets of variables and their 'parent' variables were very much hypothetical until sufficient data could be collated to test for the presence of underlying or latent concepts that would verify the suitability of the sub-variables to represent the main variables. Exploratory factor analysis was used to uncover such underlying variables. Principal

Components Analysis (PCA) was used for the factor methodology and is suitable for developing empirical summaries of the data set [167][168]

The strategy was to pool all the sub-variable constructs (questionnaire item responses) for each parent variable into a factor analysis in SPSS, extract a number of components, find 'meaning' in the extracted components, and relate the meaning to the hypothesised sub-variables The resultant factors were then used to produce standard summated scales, whose reliability was tested using Cronbach's alpha Once a reliable series of constructs were produced, they were tested for construct validity by checking the resulting items against the initial hypothesised items to ensure that important indicators for the main constructs still existed in the summated scale data

The result was that 6 factors were extracted to validly represent quality practices 3 factors were extracted to represent regulatory practices and 2 to represent business performance All these factors then formed the basis for reliable sub-scales This resulted in using 34 out of the 49 quality questionnaire items, all 16 regulatory questionnaire items and all 6 business items (see section 4 3 1) The eleven resultant variables were then easy to use to test hypotheses and generally assess the data, in that a small number of variables could be used in the analysis

It was expected that extracted factors would correlate with each other, therefore oblimin rotation (oblique) was used [167] in extraction Oblique extraction would

have produced orthogonal (unrelated) factors, which would not have been applicable for this analysis Principal components analysis produces an un-rotated pattern matrix, which is difficult to interpret Rotation produces a more meaningful final solution and shows up clearer distinctions between factors allowing for easier extraction of factors Only the rotated pattern matrices are reproduced here

4 3 1 Derivation of quality practices factors

The 49 questionnaire items (numbers 13-58 and numbers 71,74,75) used as indicators of quality were placed in the SPSS factor analysis engine The mean communality (= part of variance in common among items) for the questionnaire items was 0 56 and there were more than 30 variables, which meant that the conditions under which Kaiser's criteria for the number of factors to extract had not been met [168] Hence, a 'scree' plot was used to determine the number of components to retain This meant that the point of inflection of the scree curve as seen below in Figure 4 3 1 1 could be used as an indicator for how many components (factors) to retain to represent the initial data Using Kaiser's criteria would have yielded 11 factors (eigenvalues > 1) Using the scree plot and evaluating the additional amounts of variance accounted for by each additional factor, it was clear that 6 factors, representing 56 217% of the total variance of the data would be appropriate SPSS was then instructed to accept 6 factors The additional contributions to the total variance from taking additional factors was negligible, as indicated by the scree plot in Figure 4 3 1 1

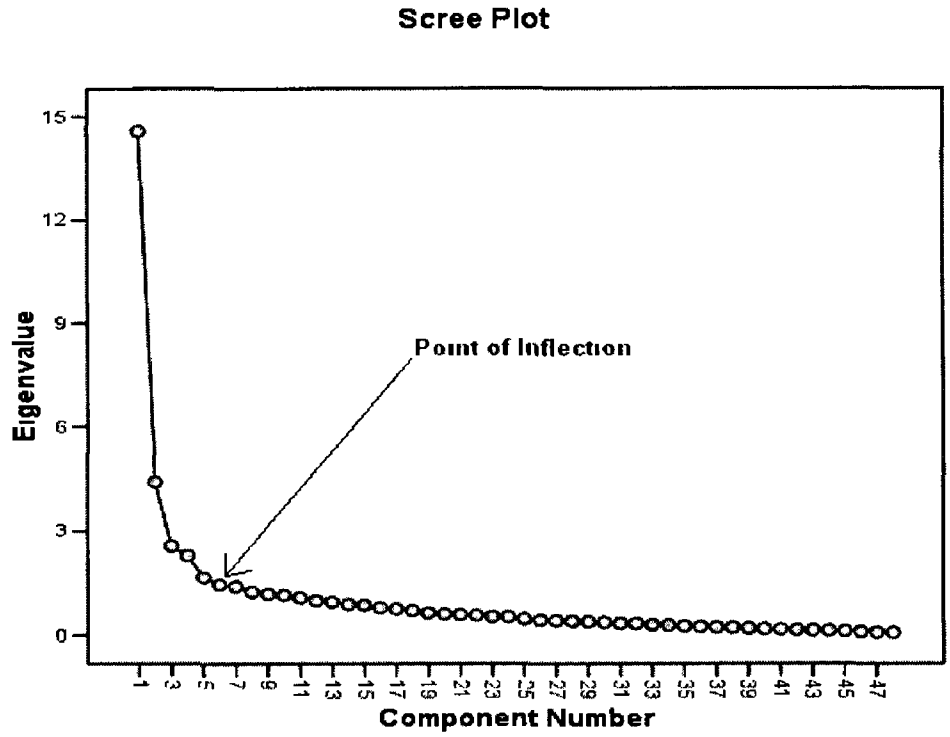


Figure 4 3 1 1 Scree plot for quality related questionnaire items

The Keiser-Meyer-Olkin (KMO) test for sampling adequacy and Bartlett's test of sphericity are standard tests for proving the suitability of factor analysis The KMO test shows sampling adequacy and must be greater than 0 6 [169] Bartlett's test verifies that the correlation matrix between all the items is not an identity matrix when it is significant For the quality items, KMO = 0 844 and Bartlett's test was significant ($p<0\ 001$) The data selected was hence acceptable for factor analysis as can be seen from the results in Table 4 3 1 1

Table 4 3 1 1 KMO and Bartlett's Test for Quality questionnaire items

Kaiser-Meyer-Olkin Measure of Sampling Adequacy		844
Bartlett's Test of Sphericity	Approx Chi-Square	3532 173
	Df	1128
	Sig	000

The rotated pattern matrix was then analysed to derive meanings from the factors and to ensure that unique (although correlated) factors were being extracted Where questionnaire items had comparable loadings across several factors, these items were dropped In total, 15 items were dropped in this manner It is arguable that these could be retained but they would then have to be included in the summated scale for each factor By removing those common items it was possible to achieve more unique factors whilst not compromising the validity of the derived factors The item loading from the derived factors needed to be 0 4 or better for inclusion in the final summated scales [167] The pattern matrix is shown below in Table 4 3 1 2 and the excluded (common) items in Table 4 3 1 3

Table 4 3 1 2 Rotated pattern matrix showing extracted components, their associated items and items / components loadings

	1	2	3	4	5	6
	General QMS	Customer Service and Leadership	Software Control	Training and HRM	Design Documentation	Use of procedures policies and standards
HighEmphasisPersDev14				0 765863		
LeadersReinforceExcellence15				0 640654		
EmployeesEmpowered16				0 730266		
EmployeesFeelValued17				0 658464		
RegQualityTraining19				0 428115		
CustomersRateQShighly20		0 542849				
CustInvolvedImprovement21		0 442159				
CustRelationsManaged22		0 582470				
ManExcellentCustInteract26		0 688158				
IssuesQuicklyComm28		0 517519				
QualPolsKnownbyStaff32						-0 491298
WorkCloselyProcedures34						-0 491248
WorkCloselyStandards35						-0 640999
RegularQMSReviews38	0 653194					
RegCompAuditsQMS40	0 720581					
SuppPerformMeasured43	0 660652					
PerformIndicUsedChange44	0 717541					
DaytodayWorkPracticesDoc45	0 577700					
CustCompSys48	0 551382					
FreqCustSatisSurveys50	0 614402					
QMSResponsibility51	0 428776					
QualAwareCampaigns53	0 656098					
MultiDepartTeams54	0 613871					
QualPlanFutureObjectives55	0 673568					
QualAgreeMainSuppliers56	0 599593					
SupplierAudits57	0 490071					
InternalPerfMeasurement58	0 783358					
EvalReqSpecsBeforeCloseout37					-0 528491	
ExtensiveInfoGatheredDevel41					-0 706511	
ExtensiveInfoGatheredTest42					-0 757369	
DirectAfterSalesTech46					-0 479994	
RevisionControlSys75			0 790599			
CodeSecurityManaged71			0 864097			
LifeCycle74			0 799314			
Alpha	0 909	0 680	0 807	0 811	0 790	0 724

The reliability coefficients (Cronbach's Alpha) are also shown for each set of scale items that would be created on the basis of the factor analysis In each case but one the Alpha value exceeds the 0 7 value normally required to indicate reliable scales [167] The second factor had an Alpha of 0 680, which was sufficiently close to 0 7 to retain Therefore a value of 0 68 is not a major infringement of the requirement For the 'design documentation' factor there was significant gain in Cronbach's Alpha if item 46 was dropped The item itself had no theoretical basis for inclusion in such a group in any case and so was not used in this factor leading to a more reliable, valid and focused factor

The common questionnaire items that were common to more than one factor were eliminated as discussed, these can be seen in table 4 3 1 3 below The items that had a loading of less than 0 4 by any factor are also shown here Items with a loading of 0 4 or less are deemed to have a weak relationship to the factor and are hence redundant The remaining items ensure that the factors remain valid None of the items in this table were considered further in the study Blank spaces on pattern matrices aid clarity in that they indicate that the loadings were less than the 0 4 cut off

Table 4 3 1 3 Rotated pattern matrix showing extracted components, and associated items with low or common loading from components

	1	2	3	4	5	6
	General QMS	Customer Service and Leadership	Software Control	Training and HRM	Design Documentation	Use of procedures policies and standards
QMSMaturity52	No Loading					
IndirectAfterSalesTech47						
ManInvolvedDecMaking23						
QualIssuesRegDiscussMeet29						
PercentTimeDocument49						
CompKnowsSupplierQMS31						
FormalGoalsObjectives18	0 403413			0 454359		
ManCommitQualImprove25		0 484726				-0 43851
QualIssuesRepTopManage24		0 404953				-0 44486
QualVeryWellPlanned30	0 400824	0 406845				
QualPolsWidelyAvail33	0 463612					-0 48118
EvalReqSpecsDuringDesign36					-0 49829	-0 40115
QMSWellKnown27		0 402569				-0 43846
RegGenWorkPracticeReviews39	0 518813					-0 41392
StaffGetJobTraining13				0 469497		-0 41792

The factors had then to be categorised in terms of the common ground that they appeared to cover Table 4 3 1 4 below explains the rationale in naming the six factors as they were

Table 4 3 1 4 Rationale for naming extracted components

Factor No	Summary Name	Rationale for Summary
1	General QMS	This factor was made up of a large number (14) of highly correlated items that all surrounded the internal operations involved in a quality management system The factor was made up of elements involving reviews and audits, use of measurement, documentation of work practices, customer complaints and feedback mechanisms, clear quality responsibilities, quality communication, planned quality and supplier management
2	Customer Service and Leadership	Whereas the General QMS factor had elements that represented the Customer management systems, the second factor was based on perceived commitment to customer service

Factor No.	Summary Name	Rationale for Summary
		and the performance of customer service. It also contained elements relating to leadership involvement in quality and the overlap between leadership involvement and customer services.
3	Software Control	This consisted of the 3 questionnaire items directly related to software control and it was expected that these items would form a distinct factor. This acted as a form of validation for the factor analysis effort.
4	Training and HRM	The fourth factor grouped 5 items together that represented human resources management and training. The five elements were essentially motivational and formed an understandable factor also.
5	Design Documentation	The three items correlated to this factor all concerned the collection and collation of documented information during the design phase.
6	Use of procedures policies and standards	This distinct factor contained elements representing knowledge and application of procedures, policies and standards.

As all factors were produced through oblique rotation it was not expected that orthogonal (unrelated) components would be produced. The verification of this can be seen in the correlation matrix in table 4.3.1.6, which shows the correlation between the summated scales produced for each factor. These summated scales were acquired by summing the item scores for each item present in the corresponding factor. Each questionnaire had a score representing each extracted factor. Table 4.3.1.6 was then achieved by looking at the correlations between scores across the survey data. SPSS also produced a between factor correlation matrix which is shown in Table 4.3.1.5. This uses SPSS derived factor scores for the survey data rather than summated scales. With the exception of some of the software quality correlations, there is a significant correlation between all the extracted quality factors, which vindicates their usage as overall quality indicators and also validates the use of oblique factor rotation [167][168].

Table 4 3 1 5 Correlation matrix for quality factor extracted components from SPSS

Component	General QMS	Customer Service Leadership	Software Control	Training HRM	Design Doc	Use Procedure Policies Standards
General QMS	1 00 0	077	238	183	- 192	359
Customer Service Leadership	077	1 000	066	276	- 216	- 197
Software Control	238	066	1 000	130	- 169	- 096
Training HRM	183	276	130	1 000	- 142	- 166
Design Doc	- 192	- 216	- 169	142	1 000	252
Use Procedure Policies Standards	- 359	- 197	- 096	- 166	252	1 000

Extraction Method Principal Component Analysis Rotation Method Oblimin with Kaiser Normalization

Table 4 3 1 6 Correlation matrix for quality factor summated scales

		General QMS	Customer Service Leadership	Software Control	Training HRM	Design Doc	Use Procedure Policies Standards
General QMS	r	1 00	0 21	0 29	0 34	0 49	0 52
	Sig		0 02	0 00	0 00	0 00	0 00
Customer Service Leadership	r	0 21	1 00	0 15	0 51	0 38	0 42
	Sig	0 02		0 09	0 00	0 00	0 00
Software Control	r	0 29	0 15	1 00	0 16	0 32	0 21
	Sig	0 00	0 09		0 09	0 00	0 02
Training HRM	r	0 34	0 51	0 16	1 00	0 35	0 49
	Sig	0 00	0 00	0 09		0 00	0 00
Design Doc	r	0 49	0 38	0 32	0 35	1 00	0 58
	Sig	0 00	0 00	0 00	0 00		0 00
Use Procedure Policies Standards	r	0 52	0 42	0 21	0 49	0 58	1 00
	Sig	0 00	0 00	0 02	0 00	0 00	

The non-significant and low correlations between software control and some of the other factors was not unexpected as software quality is a more specialised aspect of quality in general and may not necessarily be mutually inclusive.

It was important to establish construct validity at this point by comparing the literature derived indicators of quality to the resultant indicators present in the extracted factors. Table 4.3.1.7 shows how this was established.

Table 4.3.1.7: Relationship between literature derived quality indicators, representative constructs and extracted factors.

Quality variable	Proposed Item	Used?	Variable represented?	Factor
Training and Development	13	No	Yes	None
	14	Yes		Training and HRM
	19	Yes		Training and HRM
Teamwork and HR	16	Yes	Yes	Training and HRM
	17	Yes		Training and HRM
	18	No		None
Customer Focus	20	Yes	Yes	Customer Service / Leadership
	21	Yes		Customer Service / Leadership
	22	Yes		Customer Service / Leadership
	48	Yes		General QMS
	50	Yes		General QMS
Leadership	15	Yes	Yes	Training and HRM
	23	No		None
	24	No		None
	25	No		None
	26	Yes		Customer Service / Leadership
Communication	53	Yes	Yes	General QMS
	54	Yes		General QMS
	27	No		None
	28	Yes		Customer Service / Leadership

Quality variable	Proposed Item	Used?	Variable represented?	Factor
	29	No		None
Quality Planning	55	Yes	Yes	General QMS
	30	No		None
Documented Quality Policies	32	Yes	Yes	Use of procedures policies and standards
	33	No		None
Use of standards practices and procedures	34	Yes	Yes	Use of procedures policies and standards
	35	Yes		Use of procedures policies and standards
Requirements management	36	No	Yes	None
	37	Yes		Design Documentation
Reviews and Audits	38	Yes	Yes	General QMS
	39	No		None
	40	Yes		General QMS
Quality driven documented processes	41	Yes	Yes	Design Documentation
	42	Yes		Design Documentation
	45	Yes		General QMS
	49	No		None
Measurement	44	Yes	Yes	General QMS
	58	Yes		None
Service provision	46	No	No	None
	47	No		None
Quality system infrastructure	11	No	Yes	None
	51	Yes		General QMS
	52	No		None
Supplier management	31	No	Yes	None
	43	Yes		General QMS
	56	Yes		General QMS
	57	Yes		General QMS
Software control	71	Yes	Yes	Software Control
	74	Yes		Software Control
	75	Yes		Software Control

As can be seen from Table 4 3 1 7, 15 of the 16 indicators of quality (quality criteria) derived from the literature in the literature review stage of the study were represented by the final quality factors However the value of carrying out factor analysis as a basis for detecting underlying latent components in the data is clear here, as some of the constructs developed to represent a particular variable actually had a higher correlation with a different component and were hence used in the summated scale for the more appropriate construct In the pilot study simple summated scales were used which may not have been valid (although adequate for the purposes of assessing whether it was possible to analyse the pilot survey data) However the use of factors and the theoretical relationship between them and the literature deduced variables demonstrates the validity of the questionnaire items

4 3 1 1 Distribution of quality factors

Normal distributions were obtained for all the factors This was determined by using measures of skewness and kurtosis and by inspecting histograms Values with an absolute magnitude less than one represent good normality These were achieved as can be seen in Table 4 3 1 1 1 and in Figures 4 3 1 1 1 to 4 3 1 1 6 The normality, interval size and hence approximation to continuous (interval) data made the use of parametric methods more appropriate than if this approximation was not there

Table 4.3.1.1.1: Distributions for quality factors.

	General QMS	Cust Service Leadership	Software Quality	Training HRM	Design Doc	Use of Procedures Policies and Standards
Valid N	119	119	119	119	119	119
Missing N	0	0	0	0	0	0
Mean	2.17	2.94	2.27	2.57	3.18	2.71
Std. Deviation	0.68	0.52	0.93	0.67	0.65	0.67
Skewness	-0.72	-0.11	-0.87	-0.03	-0.34	-0.25
Std. Error of Skewness	0.22	0.22	0.22	0.22	0.22	0.22
Kurtosis	0.43	-0.05	0.09	-0.44	-0.39	0.17
Std. Error of Kurtosis	0.44	0.44	0.44	0.44	0.44	0.44

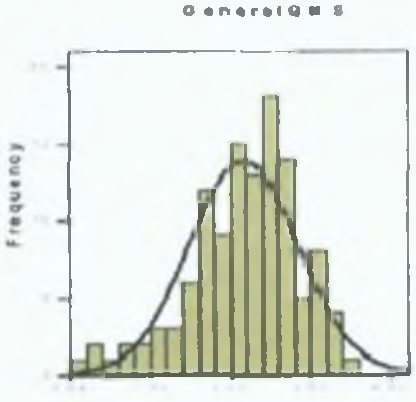


Figure 4.3.1.1.1: General QMS Distribution.

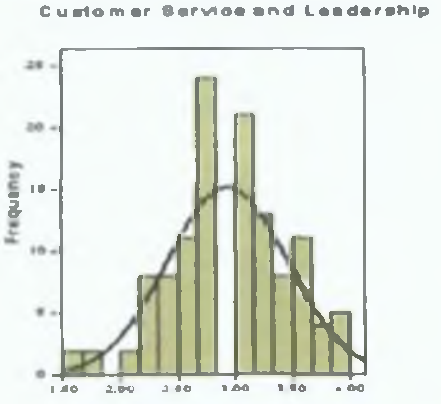


Figure 4.3.1.1.2: Customer Service / Leadership distribution.

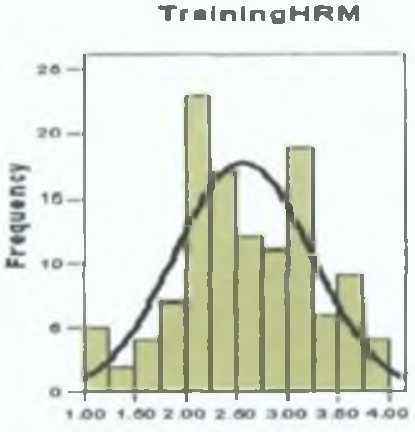


Figure 4.3.1.1.3: Training and HRM distribution.

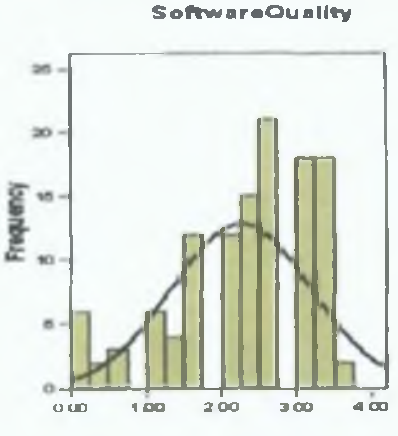


Figure 4.3.1.1.4: Software Control distribution.

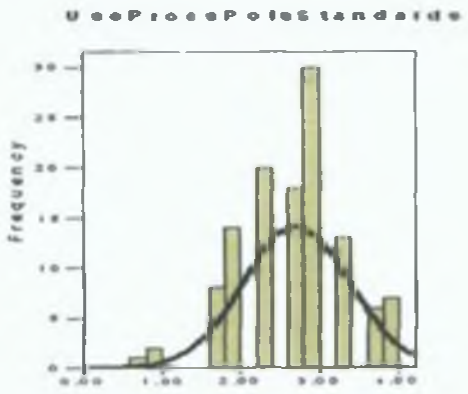


Figure 4.3.1.1.5: Use of Procedures. Policies and Standards distribution.

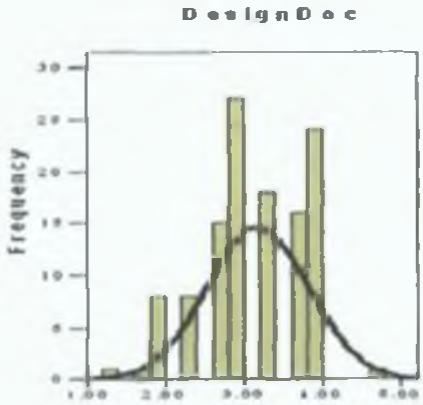


Figure 4.3.1.1.6: Design Documentation distribution.

4.3.2 Derivation of regulatory practices factors

The 16 questionnaire items (numbers 59 to 70, 77 and the grouped ERES items 72, 73 and 76) used as indicators of regulatory practices were placed in the SPSS factor analysis engine. The mean communality for the questionnaire items was 0.67 (sufficiently close to 0.7) and there were less than 30 variables which meant that the conditions under which Kaiser's criteria for the number of factors to extract had been met and could be applied to determine the amount of factors or components to retain [168].

The suitability of the data for factor analysis was assessed. The KMO value was 0.874 and Bartlett's test of sphericity was significant meaning that the test was appropriate to the data as shown in Table 4.3.2.1.

Table 4 3 2 1 KMO and Bartlett's Test for regulatory practices variables

Kaiser-Meyer-Olkin Measure of Sampling Adequacy		874
Bartlett's Test of Sphericity	Approx Chi-Square	802 658
	df	78
	Sig	000

The standard cut off eigenvalue of 1 was used for extraction Also, a 'scree' plot was used to confirm the number of components to retain This meant that the factor table (Table 4 3 2 2) and the point of inflection of the scree curve as seen below in Figure 4 3 2 1 could be used as an indicator for how many components (factors) to retain to represent the initial data Using Kaiser's criteria, 3 factors (eigenvalues > 1) were extracted, representing 66% of the total variance in the data

Table 4 3 2 2 Factor table showing cut off for Eigenvalues above 1(retained factors)

Total Variance Explained			
Component	Initial Eigenvalues		
	Total	% of Variance	Cumulative %
1	5 937266	45 67128	45 67128
2	1 553451	11 94962	57 6209
3	1 085636	8 351043	65 97194
Cut off 4	0 83809	6 446846	72 41879
5	0 758198	5 832291	78 25108
6	0 571003	4 392334	82 64341
7	0 515992	3 969171	86 61258
8	0 439361	3 379698	89 99228
9	0 380168	2 924366	92 91665
10	0 333227	2 563281	95 47993
11	0 222866	1 71435	97 19428
12	0 202769	1 559761	98 75404
13	0 161975	1 24596	100

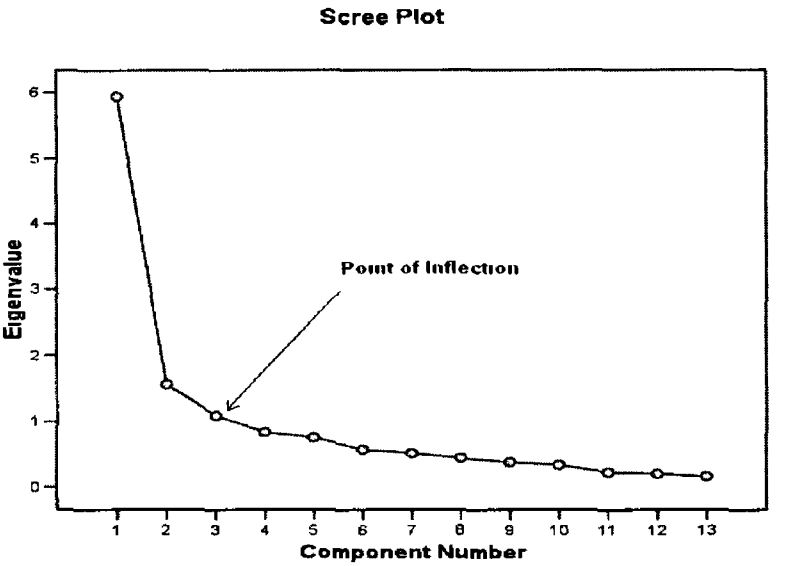


Figure 4 3 2 1 Scree plot for regulatory practices components

Using oblimin rotation, meaningful factors were then derived for use with summated scales Table 4 2 2 3 shows the derived pattern matrix with the interpreted factors and their loadings with the individual questionnaire items All the regulatory practice questionnaire items were retained for use in the summated scales As all the questionnaire items were used the scales could be deemed valid with respect to the literature derived variables for regulatory practices It should be noted that the three ERES related items (numbers 72, 73 and the five sub-components of number 76) formed a sub-scale in itself A factor analysis was carried out to verify that these represented a single factor and was successful The Cronbach's alpha for the sub-scale was 0 908

Table 4 3 2 3 Rotated pattern matrix for regulatory practices factors

	Direct Regulatory Involvement	Intrinsic Regulatory Compliance	Regulatory Documentation Availability
ERES	0 67		
SysDevKnowGMP59	0 69		
GAMPused61	0 90		
GMPmajorDesignConsider62	0 79		
SysDesDevRegCompTrng63	0 58		
ExtentGAMPoverStandards64	0 94		
FeaturesBuiltInVal65		0 73	
ValConsideredEarlyDesign66		0 83	
QMSbasedRegReq67		0 69	
DesDocWellDocAnyway60		0 64	
RegCompAuditsProd70		0 57	
DesignDocAvail68			0 82
ValDocAvail69			0 67
Alpha	0 87	0 75	0 76

The reliability of the sub-scales is also evident from the values of Cronbach's alpha achieved, which were above 0 7 in all cases The explanation of the regulatory factors is detailed in Table 4 3 2 4

Table 4 3 2 4 Meaning of regulatory factors

Factor No	Summary Name	Rationale for Summary
1	Direct Regulatory Involvement	This factor contained questionnaire items that required direct regulatory knowledge and application of GAMP, 21 CFR Part 11, and the GMPs
2	Intrinsic Regulatory Compliance	This factor involved inherent components of regulatory compliance such as compliance audits, validation, and documentation of design work for regulatory purposes
3	Regulatory Documentation Availability	This factor contained 2 items that were solely about the extent of availability of design and validation documentation

The correlation between the derived factors and between regulatory scales shows that strong cross correlations existed, demonstrating the usefulness of oblimin rotation for this data Again, as for the quality factors, SPSS produced a correlation matrix using its factor scores The summated scale correlation matrix was acquired by summing the items related to each factor Tables 4 3 2 5 and 4 3 2 6 show the factor correlations and scale correlations respectively

Table 4 3 2 5 Factor Correlations for regulatory variables

Component	IntrinsicRegCompliance	RegDocAvailability	DirectRegInvolvement
IntrinsicRegCompliance	1 00	42	23
RegDocAvailabilit	42	1 00	290
DirectRegInvolvement	23	29	1 00

Table 4 3 2 6 Scale Correlations for regulatory variables

		IntrinsicRegCompliance	RegDocAvailability	DirectRegInvolvement
IntrinsicRegCompliance	Pearson Correlation	1	47(**)	51(**)
	Sig (2-tailed)		000	000
RegDocAvailability	Pearson Correlation	47(**)	1	51(**)
	Sig (2-tailed)	00		00
DirectRegInvolvement	Pearson Correlation	51(**)	51(**)	1
	Sig (2-tailed)	000	000	

** Correlation is significant at the 0 01 level (2-tailed)

4.3.2.1 Distribution of regulatory factors

Normal distributions were obtained for all the regulatory factors. This was determined by using measures of skewness and kurtosis and by inspecting histograms. Values with an absolute magnitude less than one were achieved again represent good normality. These can be seen in Table 4.3.2.1.1. and in Figures 4.3.2.1.1 to 4.3.2.1.3.

Table 4.3.2.1.1: Distributions for regulatory factors.

		DirectRegInvolvement	IntrinsicRegCompliance	RegDocAvailability
N	Valid	118	118	118
	Missing	1	1	1
Mean		2.2294	2.2475	2.1186
Skewness		-.338	-.310	-.307
Std. Error of Skewness		.223	.223	.223
Kurtosis		-.986	-.388	-.944
Std. Error of Kurtosis		.442	.442	.442

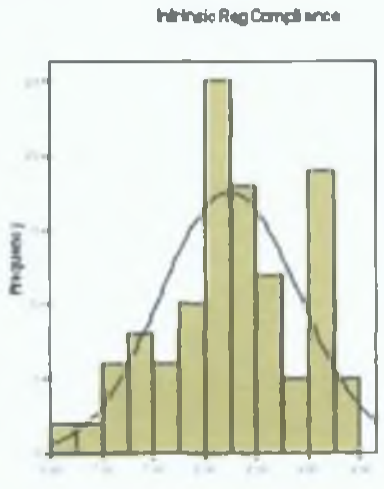


Figure 4.3.2.1.1: Intrinsic Regulatory compliance distribution

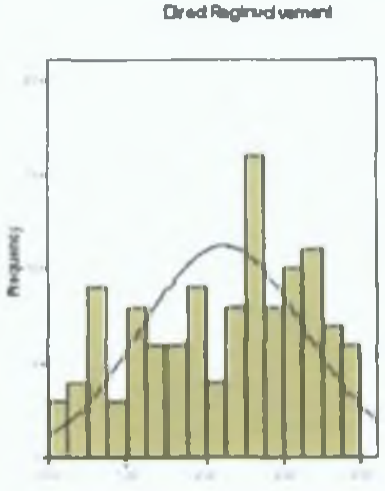


Figure 4.3.2.1.2: Direct Regulatory compliance distribution

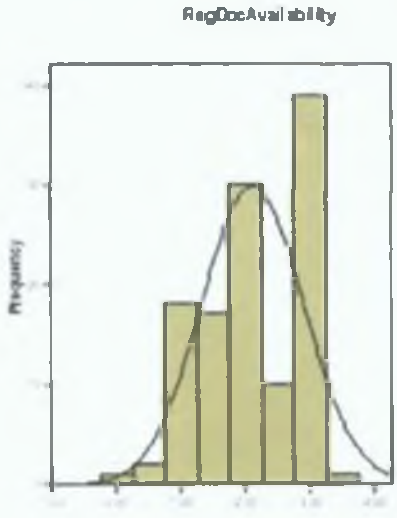


Figure 4.3.2.1.3 Regulatory documentation availability distribution.

4.3.3 Derivation of business performance factors

The 6 questionnaire items used as indicators of business performance (number 79 to 84) were placed in the SPSS factor analysis engine. The mean communality for the questionnaire items was 0.68 and there were less than 30 variables which meant that the conditions under which Kaiser's criteria for the number of factors to extract had been met and could be again applied to determine the amount of factors or components to retain [168].

The suitability of the data for factor analysis was assessed. The KMO value was 0.684 (above the required 0.6 for sampling adequacy) and Bartlett's test of sphericity was significant meaning that the test was appropriate to the data as shown in Table 4.3.3.1.

Table 4 3 3 1 KMO and Bartlett's Test for business performance variables

Kaiser-Meyer-Olkin Measure of Sampling Adequacy		684
Bartlett's Test of Sphericity	Approx Chi-Square	245 374
	df	15
	Sig	000

Two factors were derived from the data representing 67 9% of the total variance using the factor table as shown in table 4 3 3 2 below Again Kaiser's criteria was used to retain factors, the goal being to represent the data by the fewest possible number of components, which represent an acceptable amount of the total variance

Table 4 3 3 2 Factor table showing cut off for Eigenvalues above 1(retained factors)

Total Variance Explained			
Component	Initial Eigenvalues		
	Total	% of Variance	Cumulative %
1	2 784047	46 40078	46 40078
2	1 288412	21 47353	67 8743
Cut off 3	0 78521	13 08684	80 96114
4	0 597051	9 950851	90 91199
5	0 352116	5 868603	96 7806
6	0 193164	3 219403	100

With only 6 questionnaire items the scree plot was not a very useful indicator as no obvious point of inflection was shown The oblimin rotation produced two meaningful factors, one related to the items which were clearly surrounding market share and competitiveness and the other related to changes in profit and sales Both can be seen with their loadings on the questionnaire items in the rotated pattern matrix in table 4 3 3 3

Table 4 3 3 3 Rotated pattern matrix for business performance factors

	Market Share / Competitiveness	Profit and Sales Increase
ProfitLevelchange5yrPharma80		0 795857
SalesVolChange5yrPharma81		0 814073
NewProdSalesPharma2yr82		0 816769
MSchange5yrPharma79	0 507938	
MarketShareRelative83	0 933486	
OverallCompPositionRel84	0 952175	
Alpha	0 755	0 755

The scale reliabilities for the 2 extracted factors were good, with each 3-item summated scale yielding a Cronbach's alpha of 0 755 All 6 questionnaire items were retained for the 2 remaining variables, which was a positive indicator for the validity of the scales and factors The first extracted factor related to Market share and competitiveness and the second to changes in sales and profitability in relation to expectations The factors were hence named 'Market Share / Competitiveness' and 'Profit and sales increase' The factors, using SPSS factor scores, had a positive correlation (pearson's r) of 0 360 and the summated scales had a positive correlation of 0 359 significant at the p=0 01 level

4 3 3 1 Distribution of business performance variables

Normal distributions were obtained for both business variables as can be seen from the skewness and kurtosis values in table 4 3 3 1 1 and the histograms in figures 4 3 3 1 1 and 4 3 3 1 2

Table 4.3.3.1.1: Distribution of business performance variables.

		Market Share / Competitiveness	Sales / Profit Improvement
N	Valid	118	118
	Missing	1	1
Mean		3.3418	1.9492
Std. Deviation		1.08994	.54018
Skewness		-.421	-.092
Std. Error of Skewness		.223	.223
Kurtosis		-.219	.271
Std. Error of Kurtosis		.442	.442

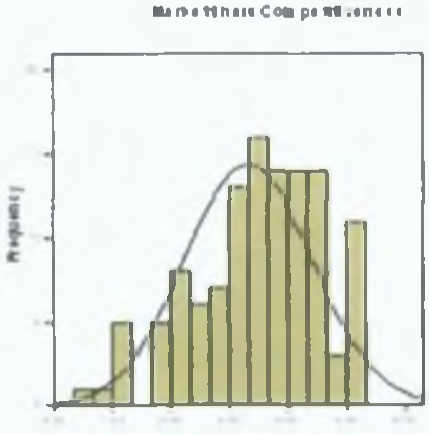


Figure 4.3.3.1.1: Market Share / Competitiveness distribution.

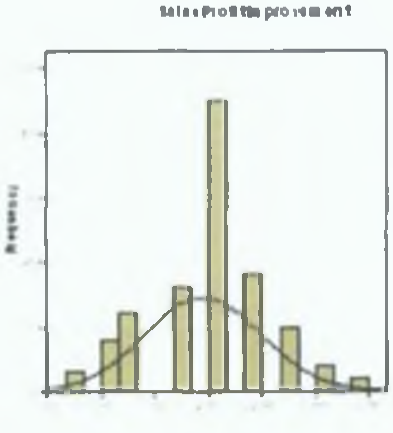


Figure 4.3.3.1.2 Profit / Sales Improvement distribution.

4.4 Central hypothesis examination and explorations

The relationships between the factors were assessed using correlation analysis. Parametric tests were used as the criteria under which they could be employed were satisfied [167][168]. Stepwise multiple-regression was then used as the multivariate technique to assess the unique contribution of independent quality and regulatory

factors to the dependent business factors The categorical background variables were then assessed to check for and to illustrate sub-group differences

4 4.1 Correlations between the quality, regulatory and business factors

Table 4 4 1 1 shows Pearson's r values for the all the quality, regulatory and business factors with the significant correlations (p< 05 and p< 01) highlighted The inter-correlations within each factor group were expected and have already been identified in the factor analysis

Of 18 possible correlation events between the three regulatory factors and the six quality factors, 16 had positive significant correlations The two exceptions were those between Customer Service and Leadership and Regulatory Documentation Availability and between Training and HRM and the same regulatory factor In general though it can be said that regulatory practices and quality practices are correlated (H2) although no determination of causation could be made

The correlation between business factors and quality factors was not so numerous Market Share and Competitiveness had a positive modest correlation with General QMS and had a low positive correlation with Training and HRM, and Use of Procedures, Policies and Standards Sales and Profit improvement had a low positive correlation with General QMS What this meant was that H1 could only be

partially accepted in that certain aspects of quality practices are correlated to certain aspects of business practice

There were low to modest positive correlations between the three regulatory practice factors and market share, and between Intrinsic Regulatory involvement and Profit and Sales improvement This meant that H3 could also only be partially accepted

Table 4.4.1.1 Correlation analysis (to 2 significant figures) showing significant relationships within and between factor groups.

		Quality						Regulatory			Business	
		GeneralQMS	CustServLeadership	SoftwareControl	TrainingHRM	DesignDoc	UseProcsPolsStandards	DirectRegInvolvement	IntrinsicRegCompliance	RegDocAvailability	MarketShare Competitiveness	SalesProfitImprovement
GeneralQMS	Pearson Correlation	1.00	0.21	0.29	0.34	0.49	0.52	0.26	0.60	0.23	0.41	0.22
	Sig. (2-tailed)		0.02	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.02
CustServLeadership	Pearson Correlation	0.21	1.00	0.15	0.51	0.38	0.42	0.28	0.21	0.13	0.12	0.02
	Sig. (2-tailed)	0.02		0.09	0.00	0.00	0.00	0.00	0.02	0.17	0.20	0.86
SoftwareControl	Pearson Correlation	0.29	0.15	1.00	0.16	0.32	0.21	0.49	0.46	0.27	0.18	0.01
	Sig. (2-tailed)	0.00	0.09		0.09	0.00	0.02	0.00	0.00	0.00	0.05	0.93
TrainingHRM	Pearson Correlation	0.34	0.51	0.16	1.00	0.35	0.49	0.34	0.28	0.13	0.22	0.09
	Sig. (2-tailed)	0.00	0.00	0.09		0.00	0.00	0.00	0.00	0.17	0.02	0.34
DesignDoc	Pearson Correlation	0.49	0.38	0.32	0.35	1.00	0.58	0.26	0.51	0.24	0.16	0.02
	Sig. (2-tailed)	0.00	0.00	0.00	0.00		0.00	0.01	0.00	0.01	0.09	0.81
UseProcsPolsStandards	Pearson Correlation	0.52	0.42	0.21	0.49	0.58	1.00	0.38	0.50	0.28	0.29	0.10
	Sig. (2-tailed)	0.00	0.00	0.02	0.00	0.00		0.00	0.00	0.00	0.00	0.26
DirectRegInvolvement	Pearson Correlation	0.26	0.28	0.49	0.34	0.26	0.38	1.00	0.51	0.51	0.31	0.02
	Sig. (2-tailed)	0.00	0.00	0.00	0.00	0.01	0.00		0.00	0.00	0.00	0.84
IntrinsicRegCompliance	Pearson Correlation	0.60	0.21	0.46	0.28	0.51	0.50	0.51	1.00	0.46	0.36	0.24
	Sig. (2-tailed)	0.00	0.02	0.00	0.00	0.00	0.00	0.00		0.00	0.00	0.01
RegDocAvailability	Pearson Correlation	0.23	0.13	0.27	0.13	0.24	0.28	0.51	0.46	1.00	0.22	0.08
	Sig. (2-tailed)	0.01	0.17	0.00	0.17	0.01	0.00	0.00	0.00		0.02	0.38
MarketShareCompetitiveness	Pearson Correlation	0.41	0.12	0.18	0.22	0.16	0.29	0.31	0.36	0.22	1.00	0.37
	Sig. (2-tailed)	0.00	0.20	0.05	0.02	0.09	0.00	0.00	0.00	0.02		0.00
SalesProfitImprovement	Pearson Correlation	0.22	0.02	0.01	0.09	0.02	0.10	0.02	0.24	0.08	0.37	1.00
	Sig. (2-tailed)	0.02	0.86	0.93	0.34	0.81	0.26	0.84	0.01	0.38	0.00	

Significant at p=.05 level Significant at p=.01 level

4 4 2 Regression analysis

Stepwise multiple-regression was used to determine the unique contribution to each business factor from each of the independent correlated quality and regulatory factors For the Market share and Competitiveness factor, General QMS, Training and HRM, Use of Procedures, Policies and Standards, and the 3 regulatory factors were entered in Stepwise regression enters in variables with the highest contribution first and so on, eliminating any variable that does not meet criteria for inclusion related to that variable's unique contribution The SPSS regression output is shown in table 4 4 2 1 Significance levels were again low, mostly below the p=0 01 level

Table 4 4 2 1 Stepwise Regression coefficients for Market Share and Competitiveness factor with all correlated factors applied as independent variables

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig
		B	Std Error	Beta		
1	(Constant)	1 932	308		6 278	000
	GeneralQMS	654	136	411	4 829	000
2	(Constant)	1 620	324		4 999	000
	GeneralQMS	563	137	353	4 110	000
	DirectRegInvol vement	230	089	222	2 578	011

a Dependent Variable MarketShareCompetitiveness

Table 4 4 2 1 shows the stepwise entry of General QMS, followed by the combined entry of General QMS and Direct Regulatory involvement into the model

The standardized regression equation that was yielded, showing unique contribution to the dependent variable was hence

Regression Equation 1

Market Share and Competitiveness =

1.620 + 0.353 General QMS + 0.222 Direct Regulatory Involvement + e1

where e1 is the error term

The two terms deemed by the SPSS procedure to be significant enough to be included in the regression equation were General QMS and Direct Regulatory Involvement. Inclusion of further terms did not increase Market Share sufficiently when General QMS and Direct Regulatory involvement were controlled. The optimal stepwise model was hence produced. The adjusted R^2 for the equation was 0.201, that is 20.1% of the change in Market Share and Competitiveness score could be explained by the influence of General Quality Management and Direct Regulatory involvement. The F ratio for the equation was computed and was significant at the p=0.01 level, meaning that the R^2 value achieved was unlikely to be zero in the population.

As standardized coefficients have been employed, the influence of QMS is 0.353 / 0.222 = 1.6 times (not accounting for error) greater than that of Direct Regulatory Involvement. In reality this means that increasing efforts in the area of general QMS would have a greater influence on market share and competitiveness than

increasing direct regulatory involvement The influence of direct regulatory involvement however was still found to be substantial however It is noted that the eliminated independent terms in the equation are partly taken account of in that they are all significantly correlated with at least one of the two retained independent terms

The resulting Equation 1 was crucial to partially support the hypotheses H1 and H3 in that one facet of business performance, market share and competitiveness, is positively influenced by general quality management systems and direct regulatory involvement

For the Profit and Sales improvement factor, the General QMS and Intrinsic Regulatory Compliance factors were input as independent variables into the stepwise procedure The coefficients for the resulting equation are shown in Table 4 4 2 2 Again, the model was significant at the p=0 01 level

Table 4 4 2 2 Stepwise Regression coefficients for Sales and Profit Improvement with all correlated factors applied as independent variables

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig
		B	Std Error	Beta		
1	(Constant)	1 520	171		8 870	000
	IntrinsicRegCompliance	191	073	237	2 612	010

a Dependent Variable SalesProfitImprovement

The resulting equation was hence

Regression Equation 2

Sales and Profit Improvement =

1 520 + 0 237 Intrinsic Regulatory Compliance + e2

where e2 is the error term.

That is the influence on Sales and Profit Improvement by the independent factors could be represented adequately by the variation in Intrinsic Regulatory Compliance However, the adjusted R^2 for this equation is only 0 048 meaning that only 4 8% of the Sales and Profit improvement score could be explained by the independent factors This was still significant, however, and adds to the evidence for accepting H3

4 4 3 Influence of background variables on model

When the background variables (Length of time established, Length of time operating in Pharma, Organisation size, Complexity of Automation, Customers look for Quality Plans, Customers carry out audits and Criticality of product to end user drug quality) were added into the regression equation for the market share and competitiveness variable a different, but related regression equation emerged Table 4 4 3 1 below shows the stepwise output All the other derived quality and regulatory factors were also added to the equation in case any of them had an effect on the established relationships

Table 4.4.3.1 Stepwise Regression coefficients for Market Share and Competitiveness with all factors and background variables applied as independent variables.

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	1.899	.309		6.156	.000
	GeneralQMS	.660	.136	.416	4.863	.000
2	(Constant)	1.418	.321		4.416	.000
	GeneralQMS	.577	.131	.363	4.406	.000
	Criticality8	.173	.047	.301	3.654	.000
3	(Constant)	1.862	.372		5.009	.000
	GeneralQMS	.689	.138	.434	4.999	.000
	Criticality8	.182	.047	.317	3.899	.000
	Est1	-.206	.092	-.195	-2.256	.026

a Dependent Variable: MarketShareCompetitiveness

The resulting standardized regression equation, showing unique contribution to the dependent variable, was therefore:

Regression Equation 3

Market Share and Competitiveness =

1.862 + 0.434 General QMS + 0.317 Criticality – 0.195 Established time + e3.

where e3 is the error term.

This equation had an R^2 of 0.274 meaning that 27.4% of the market share and competitiveness score was accounted for. The existence of Established time as a moderating term (negative coefficient) in the equation is interesting but as the General QMS score has a positive correlation (0.374 significant at the p=.01 level)

with established time, the total market share and competitiveness should not be negated as time increased That is, the net effect of General QMS and Established time should be a positive contribution to Market Share as long as General QMS increases at an appropriate rate From regression equation 3 it can be seen that the contribution of a 2 1 unit change in time is the same as a one unit change in General QMS score (standardised), so as long as General QMS increases over time it should dominate the length of time established term

The other interesting entry into the equation was the 'criticality of product to end user drug quality' background variable This replaced the direct regulatory involvement term, which has moderate positive correlation (pearson's r = 0 412, significant at the p=0 01 level) with the criticality variable It would seem from this that criticality was a greater unique contributor than direct regulatory involvement This is theoretically sound as criticality can be said to drive direct regulatory involvement and intrinsic regulatory compliance The presence of criticality did not eliminate the significant importance of regulatory involvement It revealed that if criticality was held constant, then regulatory involvement did not have any significant further influence in the Market Share and Competitiveness score

It should be noted that none of the remaining background variables or other factors appeared in the regression equation, therefore length of time operating in pharma, organisation size, complexity of automation, and the extent to which customers carry out audits and look for quality plans were not moderating or intervening variables

The existence of general QMS in regression equation 3 and the theoretical and empirical relationship between criticality and regulatory involvement means that the original regression equation 1 was not a spurious one with all background variables and the remaining factors considered

When the background variables were placed into the stepwise procedure with all correlated factors to the Profit and Sales improvement factor, the following standardised equation emerged

Regression Equation 4

Sales and Profit Improvement =

1 611 + 0 302 Criticality + e4

where e4 is the error term

The SPSS output is shown below in table 4 4 3 2

Table 4 4 3 2 Stepwise Regression coefficients for Profit and Sales Improvement with all factors and background variables applied as independent variables

	Unstandardized Coefficients		Standardized Coefficients	t	Sig
	B	Std Error	Beta		
(Constant)	1 611	110		14 622	000
Criticality8	087	026	302	3 373	001

a Dependent Variable SalesProfitImprovement

Again, the criticality element dominated the equation, and was sufficient to explain the changes in Sales and Profit Improvement scores without the requirement for

Intrinsic Regulatory compliance as a term Again the positive correlation (Pearson's r = 0 302, significant at the p= 01 level) between these two terms means that although criticality would seem to have been the greater determinant, it was also a determinant of regulatory compliance and the hypothesised relationships between regulatory practices and business performance still held The R^2 for the equation increased to 9 1% which was a doubling of the contribution offered by the model before the background variables were considered

The other background variables did not appear in regression equation 4, which indicated that the established relationship was not spurious and that none of the background variables could be classed as moderating or intervening variables

4 5 Sub-group differences

To determine differences in scores across the range of categorical and ordinal background variables non-parametric difference tests were employed, which made no assumptions about the sub-group sizes or distributions Section 4 2 showed that the sub group distributions were non-normal, making non-parametric testing essential The differences were assessed for each factor in terms of each ordinal level of the background variable and for more meaningful summary groups as defined in the distribution descriptions (section 4 2) Kruskal-Wallis H-tests were used to test for between group differences and Mann-Whitney U-tests were used to isolate the differences between pairs of groups when differences existed as determined by the Kruskal-Wallis tests The influence of the ordinal sub-groups on

the hypotheses and the relationships developed had already been tested by means of multiple regression, however the information provided by the sub-group difference evaluations were a useful output from this research also

4 5 1 Differences for time established

Table 4 5 1 1 shows the Kruskal-Wallis H-test for the summary time established categories (Established <=16 years, established >16 years) A significant difference across categories was found for General QMS and Regulatory Documentation Availability scores between the two categories of time established

Table 4 5 1 1 Kruskal-Wallis H-Test for all factors using the Time Established summary background variable as a grouping variable

	GeneralQMS	CustServ Leadership	SoftwareControl	TrainingHRM	DesignDoc	UseProcsPols Standards	Direct RegInvolvement	Intrinsic RegCompliance	RegDocAvailability	MarketShare Competitiveness	SalesProfit Improvement
Chi-Square	9 59	0 03	0 19	0 88	1 35	0 65	0 41	1 01	3 84	0 33	1 02
df	1 00	1 00	1 00	1 00	1 00	1 00	1 00	1 00	1 00	1 00	1 00
Asymp Sig	0 00	0 87	0 67	0 35	0 25	0 42	0 52	0 32	0 05	0 57	0 31
a	Kruskal Wallis Test										
b	Grouping Variable Established (summary)										

The difference between companies established up to 16 years, and those in business longer was found to be significant using the Mann-Whitney U test (all Mann Whitney and Kruskal Wallis significance tests are at the p=0 05 level in this thesis)

This is illustrated in the boxplot in Figure 4.5.1.1. It was concluded from this that companies established more than 16 years had significantly higher General QMS scores that those companies established 16 years or less.

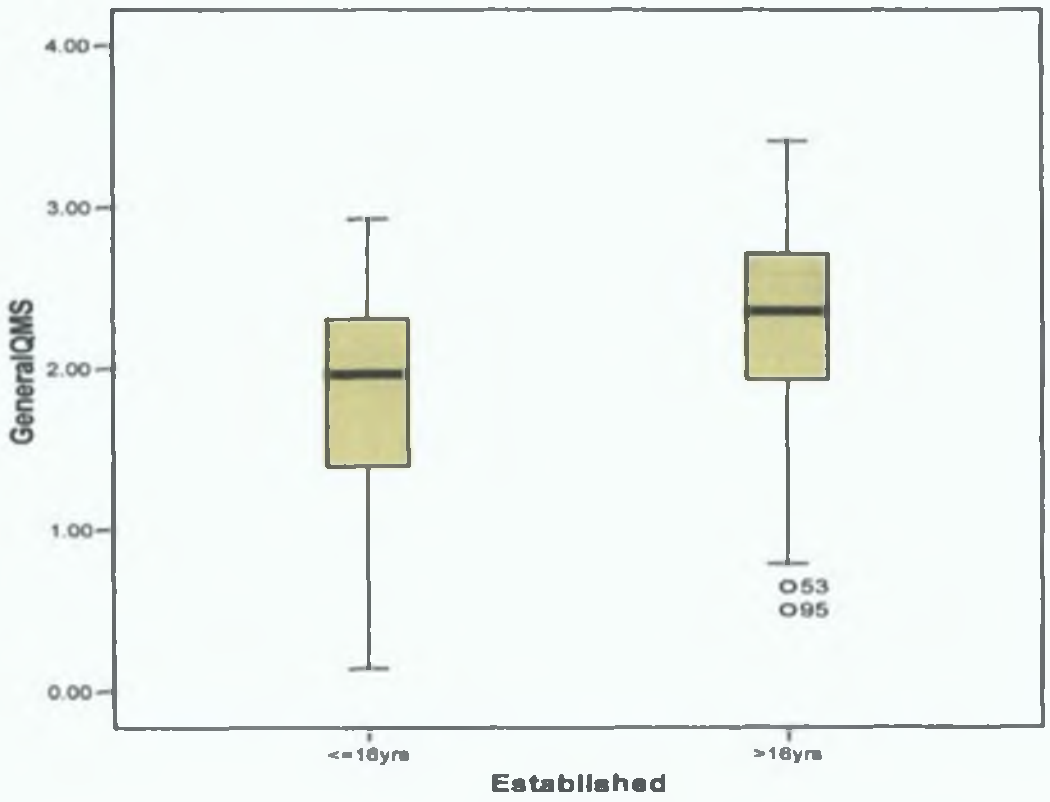


Figure 4.5.1.1 Differences for General QMS across the summarised range of 'Time Established' Categories.

For regulatory documentation availability there was also a significant difference between companies who were operating up to 16 years and those operating more. The boxplot in figure 4.5.1.2 illustrates this. As shown, regulatory documentation availability scores were higher for companies established more than 16 years.

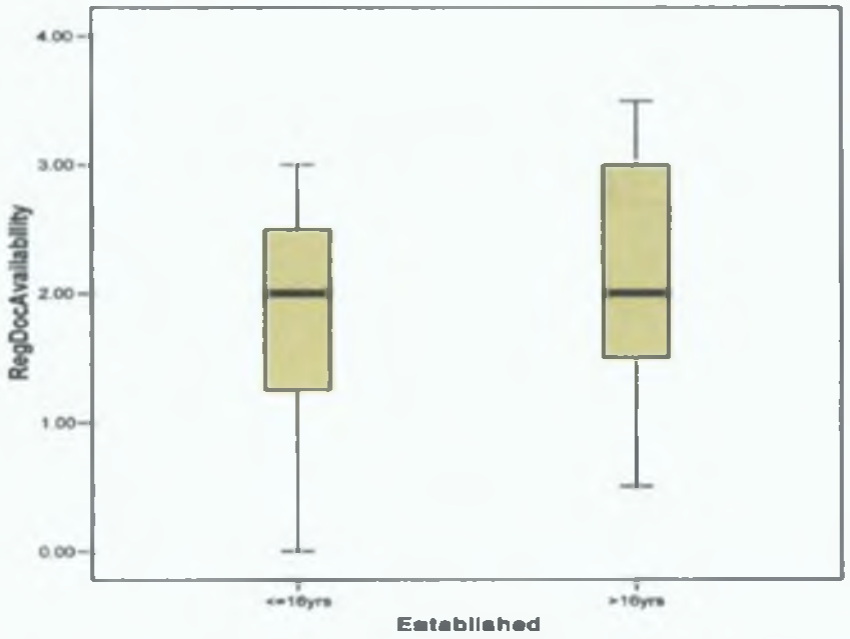


Figure 4.5.1.2 Differences for Regulatory Documentation Availability across the summarised range of 'Time Established' Categories.

The statistical significant differences in scores across groups and conclusions for the time established in pharma background variable were the same as for when total time in business was considered. Therefore the above analysis applies and reproduction of the results of the analysis was unnecessary. Time established was highly correlated with time established in Pharma (pearson's r = 0.714, significant at the p=.05 level).

4.5.2 Differences for Organisation size

The results of the Kruskal-Wallis test for differences in organisation size categories is shown in Table 4.5.2.1. Here it can be seen that there was a significant difference (at the p=.05 level) in the scores for General QMS and Market Share and

Competitiveness depending on how large a company was when assessed across the 5 ordinal levels as asked on the questionnaire The boxplot in figure 4 5 2 1 illustrate the differences for General QMS Table 4 5 2 2 shows the differences across the groups when using the summarised organisation size categories (Org size < 50, 51 to 250 and >250)

Table 4 5 2 1 Kruskal-Wallis H-Test for all factors using the Organisation Size background variable as a grouping variable

	GeneralQMS	CustServ Leadership	SoftwareControl	TrainingHRM	DesignDoc	UseProcsPols Standards	Direct RegInvolvement	Intrinsic RegCompliance	RegDocAvailability	MarketShare Competitiveness	SalesProfit Improvement
Chi-Square	29 51	6 16	3 45	9 39	3 68	2 60	3 37	6 49	5 61	11 55	5 60
df	4 00	4 00	4 00	4 00	4 00	4 00	4 00	4 00	4 00	4 00	4 00
Asymp Sig	0 00	0 19	0 49	0 05	0 45	0 63	0 50	0 17	0 23	0 02	0 23
a	Kruskal Wallis Test										
b	Grouping Variable OrgSize3										

Table 4 5 2 2 Kruskal-Wallis H-Test for all factors using the summarised Organisation Size background variable as a grouping variable

	GeneralQMS	CustServ Leadership	SoftwareControl	TrainingHRM	DesignDoc	UseProcsPols Standards	Direct RegInvolvement	Intrinsic RegCompliance	RegDocAvailability	MarketShare Competitiveness	SalesProfit Improvement
Chi-Square	21 55	3 13	0 38	2 43	0 53	0 58	0 07	1 93	2 88	7 97	2 63
df	2 00	2 00	2 00	2 00	2 00	2 00	2 00	2 00	2 00	2 00	2 00
Asymp Sig	0 00	0 21	0 83	0 30	0 77	0 75	0 96	0 38	0 24	0 02	0 27
a	Kruskal Wallis Test										
b	Grouping Variable OrgCat										

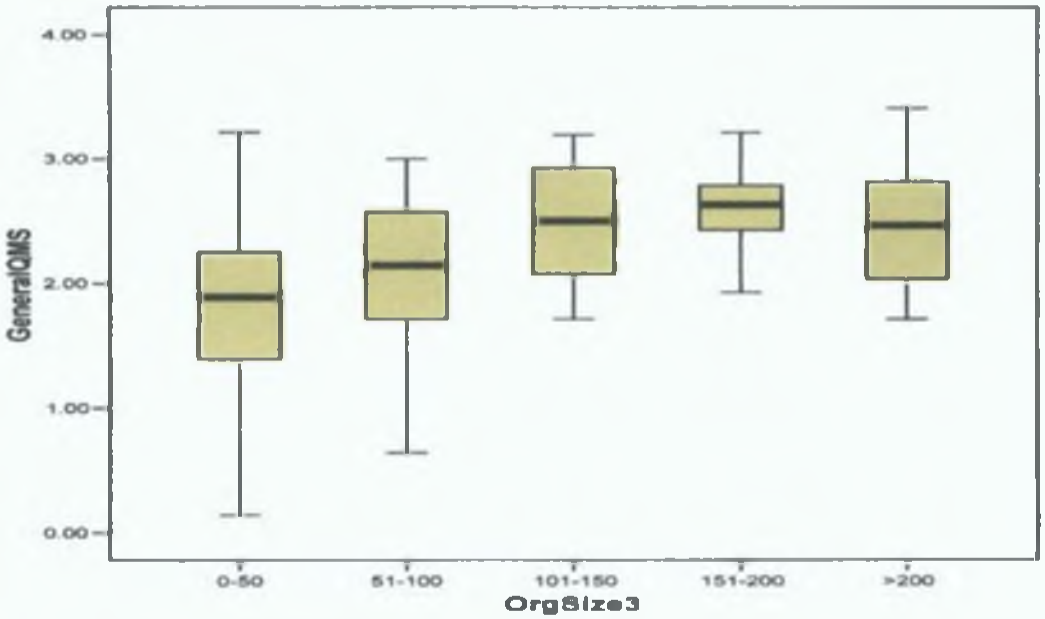


Figure 4.5.2.1 Differences for General QMS scores across the questionnaire range of Organisation size categories.

The boxplots indicated increasing levels of General QMS scores up to companies that had more than 100 employees and a general levelling off after that. This was confirmed by the Mann-Whitney outcome shown in Table 4.5.2.3 in that there were significant differences between those companies of 50 or less and those greater than 100. Also, there were significant differences between the 51-100 group and all groups with 151 employees or more. However, no differences existed between any of the groups with greater than 100 employees. This analysis was deemed to be sufficiently informative, and the summary categories did not need to be employed to give more information regarding General QMS.

Table 4.5.2.3: Outcome of Mann-Whitney difference tests for pairs of categories showing significant differences of General QMS scores between groups.

Employees	0-50	51-100	101-150	151-200	>200
0-50	-	No	Yes	Yes	Yes
51-100	No	-	No	Yes	Yes
101-150	Yes	No	-	No	No
151-200	Yes	Yes	No	-	No
>200	Yes	Yes	No	No	-

From table 4.5.2.2 it can be seen that using the summary groupings, a significant difference existed for Market Share and Competitiveness. This is illustrated in Figure 4.5.2.2.

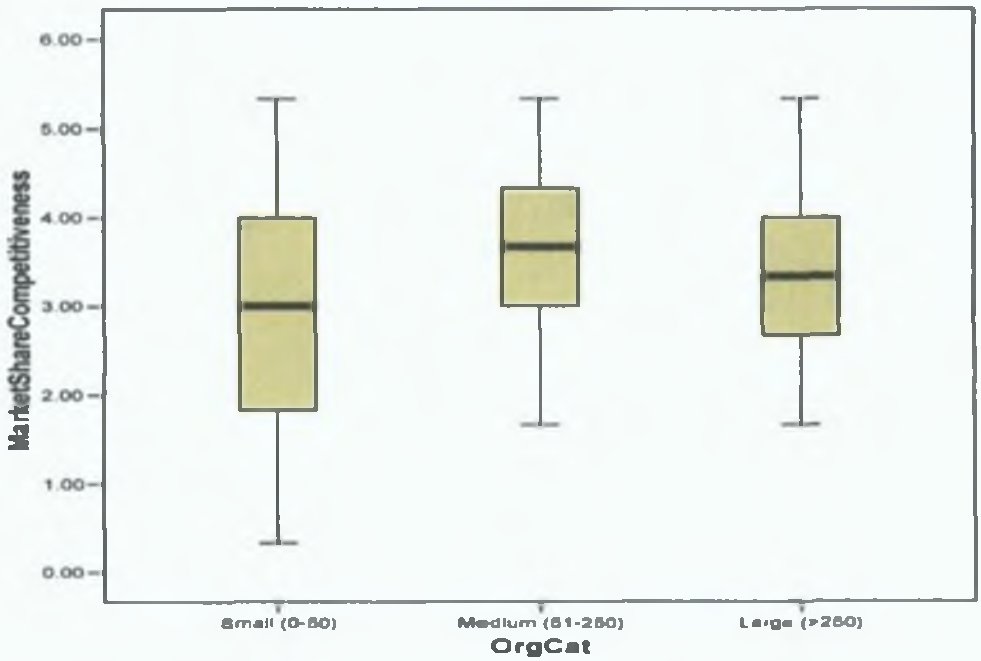


Figure 4.5.2.2 Differences for Market Share and Competitiveness scores across the summarised range of Organisation size categories.

Using Mann-Whitney tests it was found that the differences in scores existed only between small and medium organisation sizes, the latter being significantly larger. There was no significant difference found between small and large companies or

between medium companies and large companies, therefore no conclusive pattern was evident

4 5 3 Differences for complexity of automation

Table 4 5 3 1 Kruskal-Wallis H-Test for all factors using the summarised complexity of automation background variable as a grouping variable

	GeneralQMS	CustServ Leadership	SoftwareControl	TrainingHRM	DesignDoc	UseProcsPols Standards	Direct RegInvolvement	Intrinsic RegCompliance	RegDocAvailability	MarketShare Competitiveness	SalesProfit Improvement
Chi-Square	3 34	1 96	25 44	7 02	6 22	6 19	10 65	6 71	1 35	4 59	0 77
df	2 00	2 00	2 00	2 00	2 00	2 00	2 00	2 00	2 00	2 00	2 00
Asymp Sig	0 19	0 37	0 00	0 03	0 04	0 05	0 00	0 03	0 51	0 10	0 68
a	Kruskal Wallis Test										
b	Grouping Variable SummaryComplexity										

Using the Kruskal-Wallis results it was evident that significant differences existed between Software Control, Training and HRM, Design Documentation provision, Use of procedures, policies and standards, direct regulatory involvement and intrinsic regulatory compliance scores across the range of summarised complexity levels Boxplots for the six factors in relation to complexity levels are shown in figure 4 5 3 1 to figure 4 5 3 3

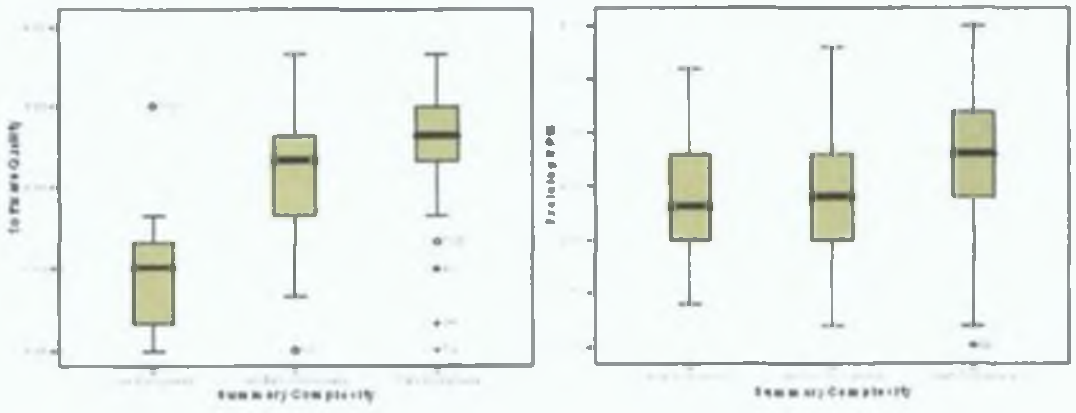


Figure 4.5.3.1. Differences between software control and Training and HRM scores across the range of summary complexity categories.

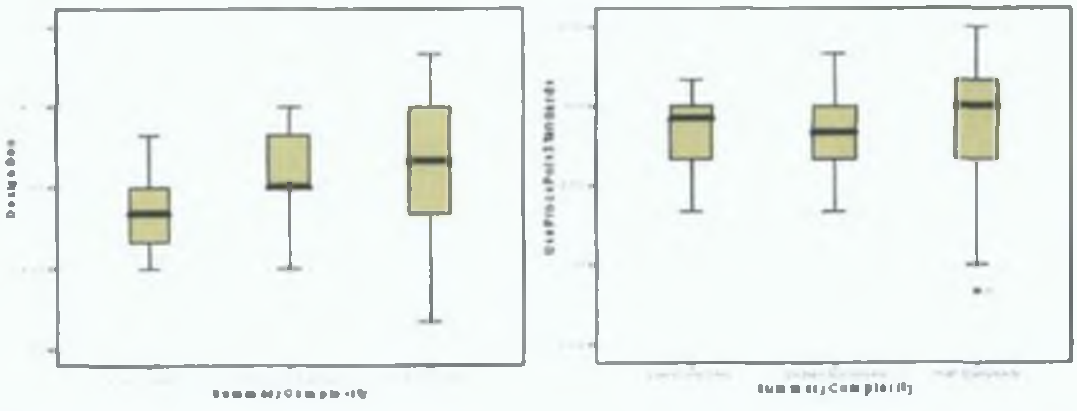


Figure 4.5.3.2. Differences across Design Documentation provision and Use of Procedures, Policies and Standards scores against the range of summary complexity categories.

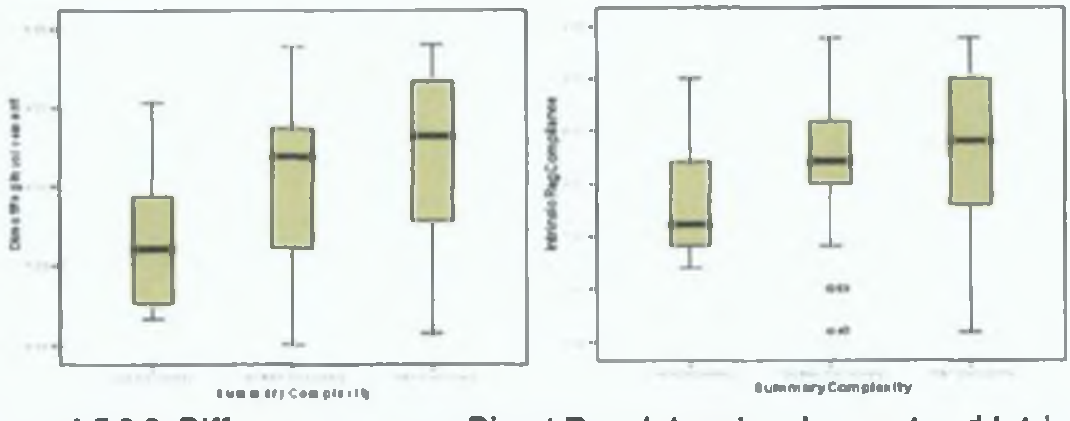


Figure 4.5.3.3. Differences across Direct Regulatory involvement and Intrinsic Regulatory Compliance scores against the range of summary complexity categories.

For all the differentiated factors an upward trend was apparent The Mann-Whitney summaries for the six factors are shown in Tables 4 5 3 2 to 4 5 3 4

Table 4 5 3 2 Mann-Whitney significant differences between pairs of summarised complexity categories for Software Quality and Training and HRM factors

	Low	Med	High
Low	--	Yes	Yes
Med	Yes	--	Yes
High	Yes	Yes	--

Software Control

	Low	Med	High
Low	--	No	No
Med	No	--	Yes
High	No	Yes	--

Training and HRM

Table 4 5 3 3 Mann-Whitney significant differences between pairs of summarised complexity categories for Design documentation provision and use of Procedures, Policies and Standards factors

	Low	Med	High
Low	--	Yes	Yes
Med	Yes	--	No
High	Yes	No	--

Design Doc provision

	Low	Med	High
Low	--	No	No
Med	No	--	Yes
High	No	Yes	--

Use of Procs/Pols/Stds

Table 4 5 3 4 Mann-Whitney significant differences between pairs of summarised complexity categories for Direct Regulatory Involvement and Intrinsic Regulatory Compliance

	Low	Med	High
Low	--	Yes	Yes
Med	Yes	--	Yes
High	Yes	Yes	--

Direct Regulatory Involvement

	Low	Med	High
Low	--	No	Yes
Med	No	--	No
High	Yes	No	--

Intrinsic Regulatory Compliance

For Software Control, there were significant differences between all three categories That is, there were significantly higher Software Control scores for each step up in complexity Similarly, Direct Regulatory involvement scores increased significantly for each increase in complexity level

Training and HRM scores were higher for high complexity automation environments than for medium, but there was no significant difference between low and high

categories, so no distinct pattern emerged here For the provision of design documentation significant differences existed between low complexity environments and medium and high levels of complexity This indicated that the complexity category had a distinct impact on the provision of design documentation In the case of Use of Procedures, Policies and Standards, there was a significant difference between medium and high complexity levels, but no difference existed between low and high or low and medium levels, again yielding no distinct pattern

For intrinsic regulatory environment, there was a significant increase in scores between low and high complexity although medium complexity levels did not influence scores significantly different from low or high complexity levels

Therefore, complexity had an important and distinctive influence in terms of software control, provision of design documentation, direct regulatory involvement and intrinsic regulatory compliance

4.5.4 Differences for Criticality

Table 4.5.4.1 shows the differences across the groups when using the summarised criticality categories (Low, Medium and High criticality).

Table 4.5.4.1: Kruskal-Wallis H-Test for all factors using the criticality of product to end user drug quality background summarised variable as a grouping variable.

	GeneralQMS	CustServ Leadership	SoftwareControl	TrainingHRM	DesignDoc	UseProcsPols Standards	Direct RegInvolvement	Intrinsic RegCompliance	RegDocAvailability	MarketShare Competitiveness	SalesProfit Improvement
Chi-Square	6.49	0.84	2.43	5.13	3.63	4.63	16.20	14.73	13.46	16.81	15.25
df	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
Asymp. Sig.	0.04	0.66	0.30	0.08	0.16	0.10	0.00	0.00	0.00	0.00	0.00
a	Kruskal Wallis Test										
b	Grouping Variable: CritCat										

Boxplots for the six factors with significant difference across groupings in relation to complexity levels are shown in figure 4.5.4.1 to figure 4.5.4.3.

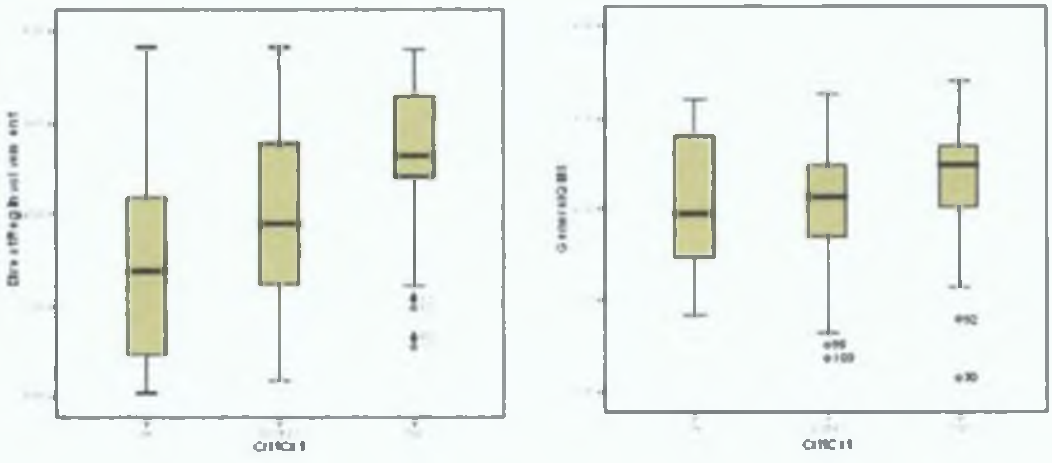


Figure 4.5.4.1. Differences across Direct Regulatory Involvement and General QMS scores against the range of summary criticality categories.

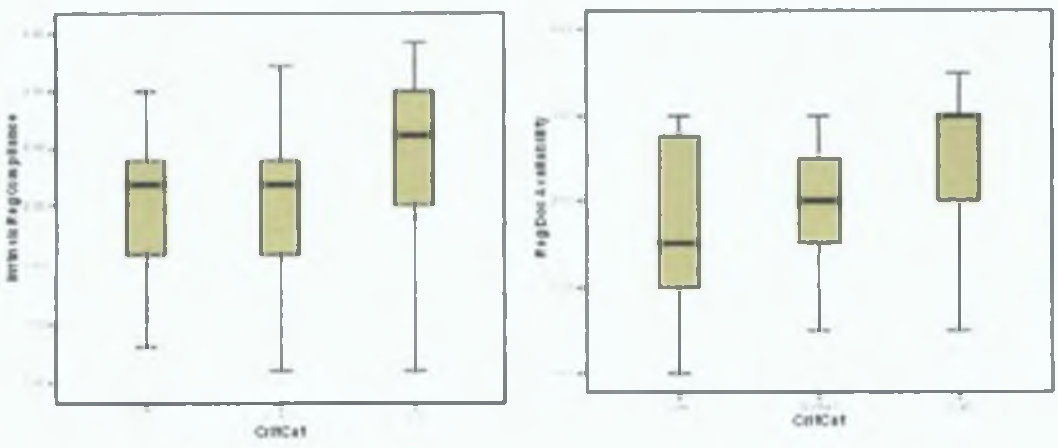


Figure 4.5.4.2. Differences across Intrinsic Regulatory Compliance scores and Regulatory Documentation availability against the range of summary criticality categories.

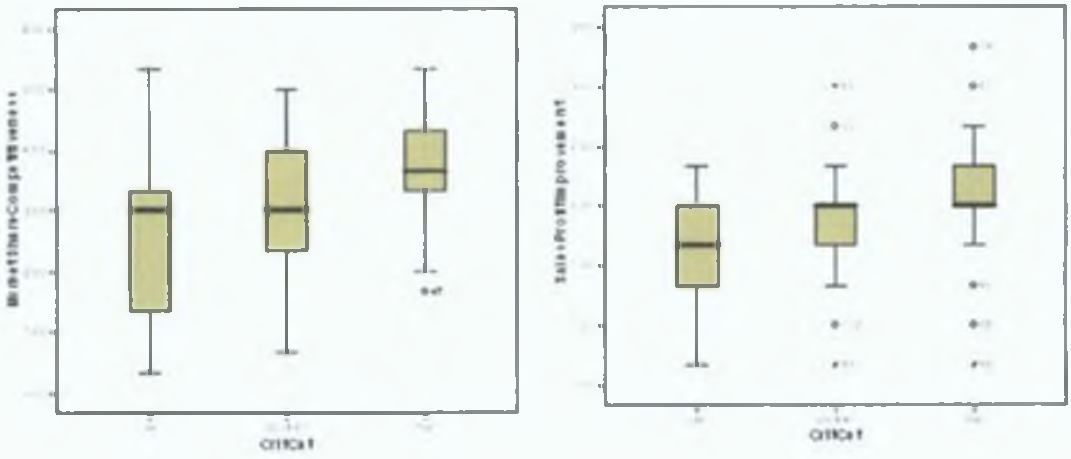


Figure 4.5.4.3. Differences across Market Share and Competitiveness and Sales and Profit Improvement scores against the range of summary criticality categories.

The influence of criticality on the data had already been assessed whilst carrying out multiple regression and was again illustrated here for the subgroups. From the boxplots an upward trend in median scores and ranges from each increase in criticality is generally evident.

Using Mann-Whitney U-tests, it was only for General QMS that there were significant differences between medium and high criticality levels Also, for General QMS, no differences existed between the low and high or low and medium levels Hence, no distinct determination could be made for this factor

For all five remaining factors the same pattern emerged from the Mann-Whitney U test There were no differences between the low and medium criticalities for any of the factors, however there were significant differences between the low and high and medium and high levels That is, for the 5 factors, high criticality distributions scored significantly higher than medium and low criticality distributions Whilst expected for the quality and regulatory factors, this was an interesting finding in terms of the business factors This is potentially attributable to higher criticality applications being subjected to more rigorous selection by pharmaceutical manufacturers making it difficult to be a player in that market, hence increasing market share, competitiveness and profitability within that sector for all proven companies

4 5 5 Differences across regulatory groupings

In assessing the categorical differences for the Regulatory Environment background variable, the summarised regulatory categories were used, as differences between the un-summarised groups were not very meaningful

The Kruskal-Wallis test is shown in Table 4 5 5 1 and differences were uncovered for the Software Control and Direct Regulatory Involvement

Table 4 5 5 1 Kruskal-Wallis H-Test for all factors using the summarised regulatory environment background variable as a grouping variable

	GeneralQMS	CustServ Leadership	SoftwareControl	TrainingHRM	DesignDoc	UseProcsPols Standards	Direct RegInvolvement	Intrinsic RegCompliance	RegDocAvailability	MarketShare Competitiveness	SalesProfit Improvement
Chi-Square	2 40	0 33	6 94	0 06	1 92	0 63	9 84	1 77	3 78	0 04	0 03
df	1 00	1 00	1 00	1 00	1 00	1 00	1 00	1 00	1 00	1 00	1 00
Asymp Sig	0 12	0 56	0 01	0 80	0 17	0 43	0 00	0 18	0 05	0 84	0 86
a	Kruskal Wallis Test										
b	Grouping Variable ShortRegCat										

The boxplots for Software Control and Direct Regulatory Environment scores are shown in Figures 4 5 5 1 to 4 5 5 2

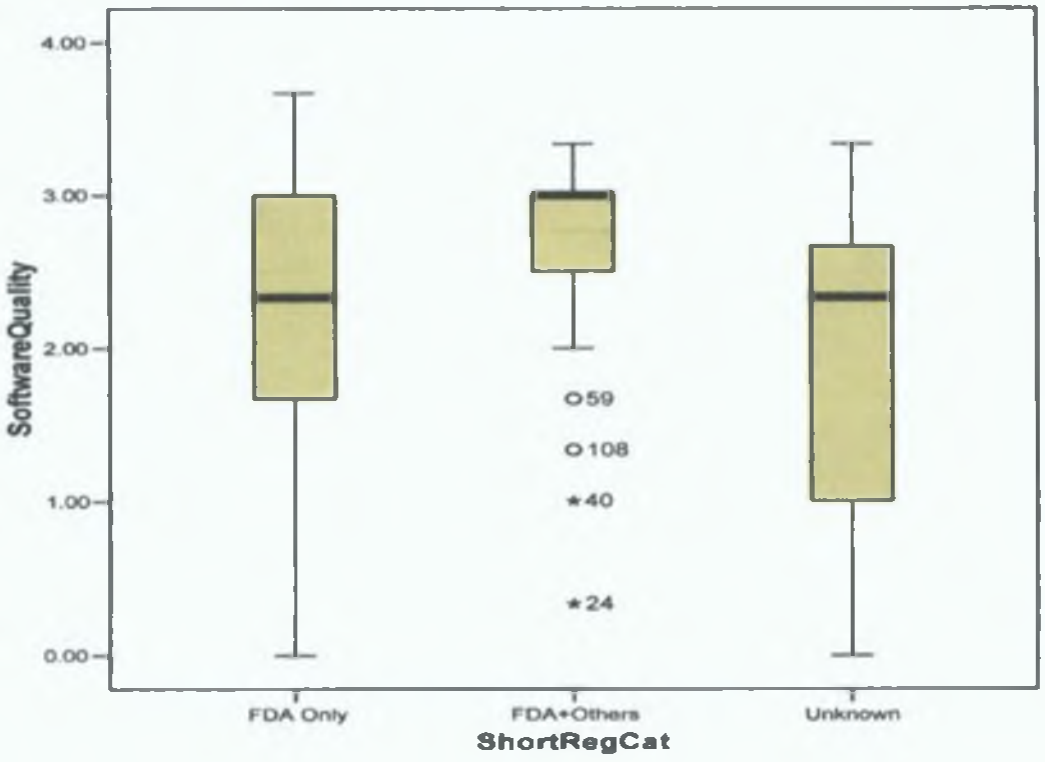


Figure 4.5.5.1. Differences across Software Control scores against the range of summary regulatory environment categories.

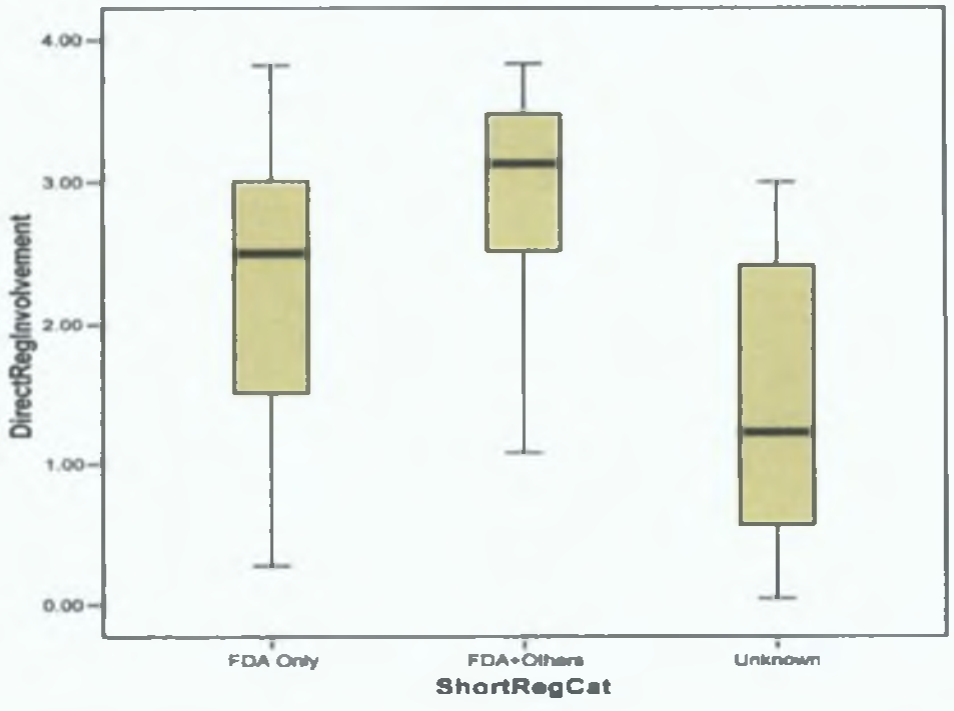


Figure 4.5.5.2. Differences across Direct Regulatory Involvement scores against the range of summary regulatory environment categories.

For the Software Control factor the scores for the FDA and others categories were significantly higher than for both the unknown category and for the FDA only category However although it was higher, the FDA only category was not significantly higher than the unknown category For the direct regulatory involvement factor, the FDA and others category was once again significantly higher than the FDA only and unknown categories The FDA only category was also significantly higher than the unknown category It was expected that when respondents did not know exactly what there regulatory environment was, then their regulatory involvement score would be lower

It was not expected that the FDA and others category would be significantly higher than for the FDA only category for the software control factor, or that the FDA only category would not be significantly higher than the unknown category for the same factor Therefore it would seem from the data that companies who worked in FDA plus at least one other regulatory environment were better at software quality than those who operated solely in FDA environments

4 5 6 Differences across quality system environment groupings

Again for the categorical differences for the Quality System Environment background variable, the summarised quality system categories were used, as differences between the un-summarised groups were not very meaningful

The Kruskal-Wallis test is shown in Table 4.5.6.1 and differences were uncovered for General QMS and Intrinsic Regulatory Compliance factors.

Table 4.5.6.1: Kruskal-Wallis H-Test for all factors using the summarised quality system background variable as a grouping variable.

	GeneralQMS	CustServ Leadership	SoftwareControl	TrainingHRM	DesignDoc	UseProcsPols Standards	Direct RegInvolvement	Intrinsic RegCompliance	RegDocAvailability	MarketShare Competitiveness	SalesProfit Improvement
Chi-Square	26.47	5.25	2.81	1.38	7.07	3.06	2.07	14.67	7.03	2.52	5.36
df	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Asymp. Sig.	0.00	0.15	0.42	0.71	0.07	0.38	0.56	0.00	0.07	0.47	0.15
a	Kruskal Wallis Test										
b	Grouping Variable: ShortQualCat										

The boxplots for General QMS and Intrinsic Regulatory Compliance scores are shown in Figures 4.5.6.1 to 4.5.6.2.

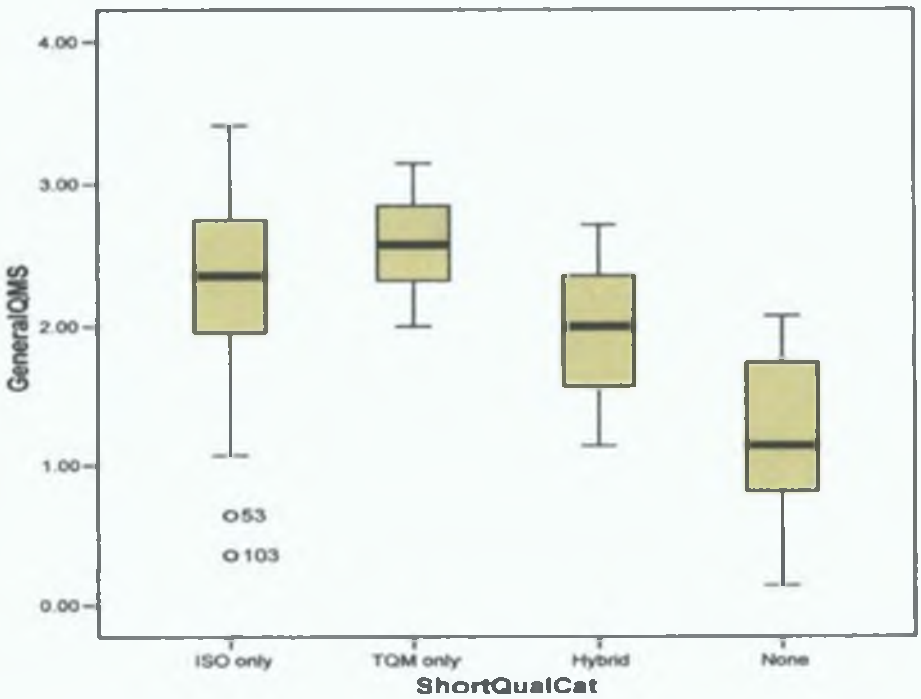


Figure 4.5.6.1. Differences across General QMS scores against the range of summary quality system environment categories.

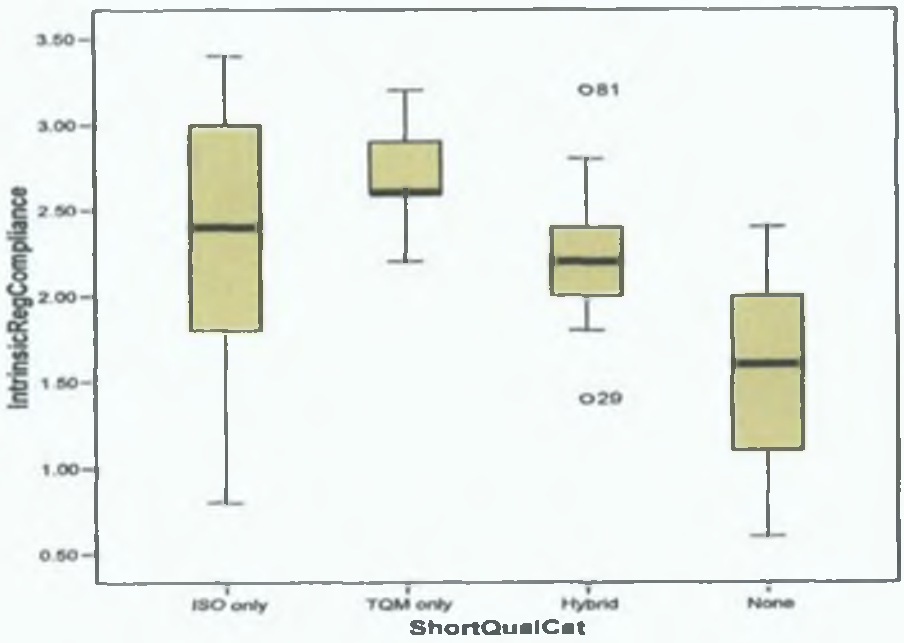


Figure 4.5.6.2. Differences across Intrinsic Regulatory compliance scores against the range of summary quality system environment categories.

From the box-plots for both differentiated factors it can be seen that scores for the ISO only and TQM only categories were higher than for when there was a hybrid or no quality system. The summary tables representing the significant Mann-Whitney U-test differences between all pairs of groups for each differentiated factor are shown in tables 4.5.6.2 and 4.5.6.3. There were no significant differences between ISO only environments and TQM only environments. There were significant differences between each of these two groups and the remaining groups with the exception of the difference between the ISO only and hybrid groups for the intrinsic regulatory compliance factor. The General QMS scores were hence higher when a formal quality management approach was in place than when such was absent or 'hybrid'. Hybrid systems scored significantly higher than where there was no system.

Table 4.5.6.2 Mann-Whitney significant differences between pairs of summarised quality system environment categories for the General QMS factor scores.

	ISO Only	TQM Only	Hybrid system	None
ISO Only	--	No	Yes	Yes
TQM Only	No	--	Yes	Yes
Hybrid system	Yes	Yes	--	Yes
None	Yes	Yes	Yes	--

Table 4.5.6.3. Mann-Whitney significant differences between pairs of summarised quality system environment categories for the intrinsic regulatory compliance factor scores.

	ISO Only	TQM Only	Hybrid system	None
ISO Only	--	No	No	Yes
TQM Only	No	--	Yes	Yes
Hybrid system	No	Yes	--	Yes
None	Yes	Yes	Yes	--

4.6 Summary of Data Analysis

The distributions were evaluated for respondents in terms of the length of time companies were established, time established in the pharmaceutical industry, organisation size, complexity of the automation used in respondent's products, criticality of the respondent's product to end user drug quality, the regulatory environment respondent's products were designed for, and the quality system environment of the respondent company. The distributions were assessed using the categories from the questionnaire and also using summarised categories that gave more meaning to the survey data. It was desirable to have a sufficient number of responses across the range of subgroups for each background variable so that the presence of any non-response bias could be evaluated. It was found that sufficient

data existed across all the groups in a given distribution to allow further analysis and to allow generalisation of findings (external validity) The summarisation into a lower number of sub-categories contributed to safer generalisation possibilities, as more cases were present per category

Factor analysis was then used on the quality, regulatory and business related questionnaire items to reduce the data into a smaller number of manageable and meaningful factors Principal Component Analysis with Oblique rotation yielded 6 quality factors, 3 regulatory factors and 2 business factors The factors were used as the basis for summated scales, which were all found to be reliable in terms of internal consistency using Cronbach's alpha The summated quality scores were found to be positively correlated with the regulatory scores Specified quality scores were found to be correlated to the business scores Similarly, specified regulatory scores were positively and significantly correlated with one of the two business factor scores These relationships meant that the null hypotheses H1o, H2o and H3o could not be rejected based on correlation output

Multivariate analysis was then employed to determine predictors and the unique variance contributed by individual independent summated scores for each factor When all the quality and regulatory variables were input to the stepwise regression procedure with the Market Share and Competitiveness factor score as the dependent variable it was found that General Quality Management System scores and Direct Regulatory Involvement could be used as predictors This model

accounted for 20 0% of the change in Market Share and Competitiveness Intrinsic Regulatory Compliance could be used as a predictor of Profit and Sales increase scores, but only 4 8% of the change in this business score could be attributed to the model The regression equations showed that the predictors (General QMS, Direct Regulatory Involvement and Intrinsic Regulatory compliance) could essentially be used to represent all the data in terms of positive effects on business performance As the predictors were positively correlated with many other factor scores, this did not mean that the other factors were not determinants of business success, merely that they could be represented by the predictors The regression equations were significant and offered further support to the acceptance of the hypothesis (H1 and H3)

Stepwise regression was also used to determine the impact of background variables on the established relationships For both regression relationships the regulatory component was replaced by criticality, in that criticality could be used to represent the regulatory factors For the Market Share and Competitiveness dependent variable, General QMS was retained as the dominant predictor but there was a moderating effect by the time established in business background variable As General QMS was dominant and positively correlated to time established, the predictors still showed a significant positive change in the dependent business factor The R^2 for the equation rose to 0 274 or 27 4% meaning that 27 4% of Market Share and Competitiveness scores were accounted for by the predictors, i e Criticality could better predict the dependent variable by 7 4% For the Profit and

Sales improvement factor score R^2 increased to 9 1% which was almost a doubling in the contribution from the predictors Hence criticality could give a better representation than regulatory factors for both business factors Again, this did not diminish the importance of the regulatory scores, it merely showed that another predictor could represent them

Sub-group differences were then assessed for each of the background variables using both the questionnaire categories and the summarised categories developed during the distribution review Sub group behaviour was identified using non-parametric testing between groups For the time established background variable, significant differences were found between intrinsic regulatory compliance and general QMS scores across groups For the former no useful pattern emerged however for the latter it was found that General QMS scores were significantly higher for companies in business for longer than 16 years

For organisation size, it was found that General QMS scores were significantly lower for small companies when compared to medium and large companies However, there were no significant differences between medium sized companies and larger ones

Complexity of automation levels yielded significant differences in Software Control, Training and HRM, Design documentation Availability, Use of Procedures, Policies and Standards and the two regulatory scores For Software Control there was a

significant increase in scores for each step up in complexity from low to medium to high No distinct pattern emerged for Training and HRM or for Use of Procedures, Policies and Standards The impact on Design documentation availability was also significant in that there were higher scores for high complexity levels than for lower complexity levels or medium complexity levels For the regulatory compliance scores there were significant score increases between low and high complexity levels but medium levels did not differ significantly from either adjacent level

When the criticality background groups (low to medium to high) were assessed, no distinct pattern emerged for the General QMS score differences For Direct Regulatory Involvement, Intrinsic Regulatory Compliance, Regulatory Documentation availability, Market Share and Competitiveness and Sales and Profit Improvement, high criticality distributions scored higher than for medium and low criticality distributions The differences in business scores were conjectured to be due partly to the type of selection process operated by the pharmaceutical manufacturing industry

Across the summary regulatory groupings Software Control scores for 'FDA and others' were higher than for 'unknown' and 'FDA only' scores The FDA only category was not significantly higher than the unknown category, but the range for the FDA only category was quite broad

For the Quality Management environment background variable significant differences existed between the ISO only or TQM only categories with when hybrid or no QMS was in place, when considered for the General QMS and Intrinsic Regulatory Compliance factors

Chapter 5: Discussion, Conclusions and Outlook

The focus of this research was to ascertain the relationships between quality practices and regulatory practices, between quality practices and business performance and between regulatory practices and business performance The study revealed that significant relationships existed between aspects or factors of these three variables These relationships and absence of other relationships could be used to determine whether the study hypotheses could be rejected or upheld

5 1 Quality Practices and regulatory practices

Although no evidence could be found of research into the relationships between quality practices and regulatory practices, the nature of what are deemed to be regulatory practices are essentially quality system manifestations Therefore correlations between the quality management, or general quality practices elements of the entire quality effort, and the GMP elements of the entire quality effort should have existed in a symbiotic way in the findings of this research The correlations detailed in this discussion are elaborated on in order to give a general picture of the interdependence of GMPs and quality management systems, it is not suggested that where two variables or factors are correlated, that this relationship is due to a unique contribution, and no other variables or factors are involved No suggestion of causation was intended, as the hypotheses, results and the literature imply mutually improving influences between quality practices and regulatory practices The Good Manufacturing Practice regulations themselves [1][2][3][37][58][59][70] state

requirements for quality systems implementations and 'The Orange Guide' [5] defines GMP as being an element of quality assurance Many of the regulatory features have a basis, and source, in the quality standards themselves For example, the availability of documentation which is required by the regulations is also a requirement of the ISO 9001 2000 and ISO 9000-4 2004 under the documentation and record management and product realisation sections Validation is also a requirement of these standards under the 'Design and development planning, review and validation' sections The GAMP guide [13] heavily leverages a series of international quality standards for development and testing of automated (software based) systems Regulatory design reviews are essentially an evaluation of the development and realisation of software against the quality requirements, which is again a quality system requirement of the international quality standards (such as the ISO9000 series), as is the use of the Software Development Life Cycle (SDLC) approach

The details of the requirements set out in the electronic records and electronic signatures regulations are once again quality requirements for development and control of systems where data integrity is paramount and compliance with other standards would yield the same level of software quality Perhaps the only requirement that is truly unique is the regulatory requirement for the availability of developer source code [51] The regulations in essence then provide a focused set of quality requirements for the manufacture of medicinal product and for development of systems used in their manufacture Therefore the extent and

strength of the correlations found in this work between quality and regulatory practices were expected, and the survey was a means of confirmation and validation rather than one of discovery for these two variables

However, it needs to be stated that the regulatory factors as extracted in this study were distinct That is, for the 'Direct regulatory involvement' factor, all the elements that comprised it had a direct relationship to the GMPs or to GAMP (a means of compliance with GMPs) Although a means of achieving high quality, GMPs themselves are not completely inherent in a general quality system It is feasible that regulatory practices and quality practices could be mutually exclusive However from this work and the appraisal of the literature, it is clear that this is not the case in practice The positive correlation between the regulatory practices factors and the quality practices factors confirms the relationship Andrews [35] states general quality management systems such as ISO can contribute to, but don't completely meet the needs of regulatory compliance He also suggests that the quality management system outlined by GAMP is appropriate to an environment producing automated systems Hence, the mutually beneficial relationships between quality management and regulatory compliance are known The two-way relationship is illustrated by Margetts [40] who says that in order to achieve regulatory compliance, a quality methods approach must be taken for software development As stated by Trill [72], the object of GMP and the quality system is the same, assurance of quality of the product for the safety and well being of the patient It follows then that a company with a higher emphasis on one will have a higher emphasis on the other

Of the 18 possible inter factor relationships between regulatory and quality practice scores, 16 yielded positive significant relationships of varying strength The 'Intrinsic Regulatory Compliance' factor, which represented those activities within companies that would result in regulatory compliance, had a Pearson's correlation of 0 60 with the 'General QMS' factor, which represented the central requirements of most quality system standards As many of the intrinsic compliance activities would have been in place as a result of direct compliance with quality standards such as ISO9001 and ISO9000-4 it would have been expected that a high correlation emerged here Similarly, the 'Use of procedures, policies and standards', 'Software Quality' and 'Design Documentation' factors had a positive correlations of around 0 50 with the Intrinsic Regulatory Compliance, for the same reasons as it had such a strong correlation with the General QMS That is, by having good quality systems practices, the intrinsic regulatory compliance efforts of a company are likely to have been positively influenced also Hence, system developers can go a long way to achieving compliance with regulatory requirements by adopting international quality standards This is supported by Foote [54] who suggests that the CMM requirements can be used to provide the same level of quality assurance that following GAMP can provide, that is substantively meeting the regulatory requirements through adopting a general (non industry specific) standard GAMP itself also alludes to this [13] Foote also outlines the comparable sections of the GAMP guidance and how it related to the ISO 9000 series, again recognising the correlation The significant moderate positive correlations between the Software Quality and regulatory

compliance factors also show this relationship That is, software quality is correlated with the regulatory compliance scores, which is the goal of those regulatory compliance practices Sharp [5] identifies GMP activities as being the focus of a greater QA effort, therefore the compliance factors should have a direct correlation with one or more facets of 'pure' quality assurance The extent of the existence of positive correlations between the group of quality practices factors and regulatory compliance factors in this work supports, and is supported by Sharp's assertions Glennon [7] also points out the closeness of general good engineering practices to the practices required by the regulators, in that the following through specific requirements of established standards, the regulatory requirements can be fulfilled in the main

The relationship between quality practices and direct regulatory practices and knowledge may in part be due to the cultural legacy of being 'good at quality', or may be in part due to having to realise a top class quality system as a result of regulatory requirements Further support is given to the interdependence of quality practices and regulatory practices by Coady and de Claire [77] whose approach to overall compliance to process control system validation requirements adopts a joint quality system and direct regulatory compliance strategy The level of correlation between general QMS was much higher when matched with intrinsic regulatory compliance than with direct regulatory involvement (r=0 60 and 0 26 respectively at the p=0 01 level) Intrinsic compliance means the practical realisation of the requirements through the quality system, whereas the direct regulatory involvement factor was

more concerned with direct knowledge and application of the GMPs (including Part 11) and use of GAMP

The dependence of regulatory compliance on sound quality systems for software is emphasised in the literature [13][25][35][39] This dependence was confirmed by these results, in that moderate positive correlations were found between the software control factor and both the direct regulatory involvement and intrinsic regulatory compliance factors Similarly, the moderate positive correlation between provision of design documentation and intrinsic regulatory compliance enhanced this finding Provision of design and test documentation as part of the software lifecycle and control elements of a quality system is advocated by GAMP [13], and by the literature in general when discussing development of systems [8][35][55]

In this study a positive correlation was found between software control and availability of regulatory documentation, which suggests that companies who employ a more formal software control system during development are better at keeping validation and design documentation The direction of this relationship is unknown although it can be stated that those who have better software control score better with regards to record and test script retention, and those who focus more highly on such retention have better software control This mutuality is inherent in analysing the quality / regulatory practices relationships Again this is consistent with the body of literature, which always states that regulatory requirements can be complied with by means of quality system manifestations, but that these manifestations cannot be

effective without good regulatory practices The sound appreciation of the regulations is necessary to have a quality system capable of compliance [51] Hence, the positive correlations between regulatory practice scores and quality practice scores from this work make sense in this context, in that better interpretation of the regulations can lead to better quality systems and better quality systems may enhance the compliance effort

The 'soft skills' side of the quality practices scores consisting of leadership, customer service, training and human resource management all had a positive correlation with direct regulatory involvement and intrinsic regulatory compliance The positive influence of these aspects of quality management on business performance as stated in the wider body of literature seems to influence the regulatory practices element also (although it is not suggested that this could be the case in the absence of other factors) In general, the influence of these quality system elements on regulatory practice is positive, although correlations are generally low in magnitude However, their influence through other aspects where they are more highly correlated such as the general quality management system, the use of practices, procedures and standards, and provision of design documentation may have a knock on positive influence It has to be stated though that as training is a regulatory requirement that the direction of influence could as easily be from the regulatory side to the quality system rather than the other way around In any case, the mutual benefits were clear once again when looking at the scores for regulatory practices and the customer service and leadership / training and HRM scores As the net

effect of these aspects is to increase overall knowledge, proficiency, customer involvement and motivation regardless of the source (i e quality system or regulatory pressures), the benefits are clearly positive in terms of regulatory compliance and quality

The moderate positive correlations between the software control factor and the direct regulatory involvement factors was expected as the constituents of the direct regulatory compliance scale consisted of some items that were based on use of GAMP, which uses lifecycle development for software and advocates software controls Similarly for the intrinsic regulatory compliance factor, testing and development documentation help make up the scale As a good software development environment would consist of good software control and testing methodology (whether required by regulatory authorities or not), the strong correlation was expected here also The correlation between general quality management system scores and intrinsic regulatory compliance scores (pearson's r = 0 60 at the p= 01 level) was considerably higher than for that between general QMS and direct regulatory involvement (pearson's r=0 26 at the p=0 01 level) This was because many of the items contributing to the intrinsic regulatory compliance scale were quality system manifestations of regulatory compliance requirements, such as validation, audits and documentation and record keeping Hence a good quality system should mean better *de facto* compliance Similarly, by applying the requirements of the regulations in practice, the quality practices of an organisation should be improved This mutuality is confirmed through this research

The moderate correlation between the provision of design documentation and intrinsic regulatory compliance was higher (Pearson's r = 0 51 at the p=0 01 level) than for that between provision of design documentation and regulatory documentation availability (Pearson's r=0 24 at the p=0 01 level) The high correlation with the former was due to the common elements of validation and regulatory required design documentation provision, with the design and validation activities that make up intrinsic regulatory compliance The low correlation with the latter factor was possibly due to the *availability* term That is, although developers document their development and testing, they do not necessarily make it available to end-users For lower risk and less complex systems this can be acceptable to drug manufacturers (as per GAMP categorisations for example), however for higher risk or more complex automated solutions, manufacturers would request better levels of design documentation from suppliers Although low, the positive significant correlation here was still important to show that provision of design documentation can contribute positively to intrinsic regulatory compliance

The 'Availability of regulatory documentation' factor was a more specific requirement than the two compliance factors in the regulatory grouping It was not correlated significantly with the 'Customer service and leadership' or 'Training and HRM' factors However, the more general quality practices factor of 'provision of design documentation' did have a positive correlation with this regulatory documentation factor The lack of correlation here was possibly due to the more specific nature of

the factor Regulatory documentation availability itself had a low correlation with the quality practices variables It is reasonable to say that the largest practical difference for almost all suppliers of systems to the pharmaceutical industry has been the additional work (in terms of creating that documentation, and making it available to the standard required by pharmaceutical customers) required for validation and validation protocol scripting and execution This goes beyond the test script requirements for non industry-specific software testing, so therefore does not tie in that closely to the normal requirements of a quality system This could explain the lack of strength in the correlation between this factor and the quality factors It is an important regulatory consideration however, and is moderately correlated with both the direct regulatory involvement score and the intrinsic regulatory compliance score (Pearson's r= 0 51 and 0 46 respectively at the p=0 01 level)

The use of procedures, policies and standards had a higher correlation with intrinsic regulatory compliance (Pearson's r = 0 50 at the p=0 01 level) than with the other two regulatory practices scores Again this is because of the nature of the intrinsic regulatory compliance factor which involves quality system manifestation as opposed to the more abstract 'knowledge based' nature of direct regulatory involvement (Pearson's r = 0 38 at the p=0 01 level) and the more specific nature of availability of regulatory documentation (Pearson's r = 0 24 at the p=0 01 level) Use of procedures and policies in particular are paramount to both regulatory compliance and to a successful quality system, so the r=0 50 correlation here was not unexpected

The aim of this section of the research was to show that where high quality practice scores existed, then high regulatory practice scores would also exist No causal exploration was required From the analysis and discussion it can be seen that regulatory factors and quality factors were indeed positively correlated, with some factors more highly correlated than others The general finding that quality and regulatory practices are mutually beneficial concurs with the inferences in the wider literature, although as stated previously, no research other than this exists to uphold it Therefore it can be stated that H2 in this work cannot be rejected, as 16 out of 18 possible relationships between quality practices and regulatory practices factors were positively and significantly correlated All regulatory factors were correlated with at least two quality factors and *vice versa*

5 2 Quality Practices, Regulatory practices and Business Performance

The general finding from the literature was of a weak positive correlation between quality management practices and business performance, whether as part of a TQM effort, ISO 9001 environment or as practices in some hybrid quality structure The purpose of this section of the research was to ascertain whether the same relationships could be determined empirically when the added dimension of regulatory practices was considered This extra dimension had to be considered in the sector of interest, developers of automated solutions for the pharmaceutical industry The models developed showed that when the quality and regulatory

variables were considered, weak to moderate relationships were found between aspects of quality management, regulatory involvement and compliance, and aspects of business performance This was consistent with the findings from the literature as discussed below The two aspects of business performance, profit and sales improvement and market share were positively correlated with several quality and regulatory practice factors to differing degrees which did much to uphold the study hypotheses although no 'simple' relationship could be extracted from the set of results It would not have been justified to say for example that all the quality practices outlined in this work contributed to business performance improvements directly, as some of the extracted factors had no direct correlation and did not figure in the stepwise regression models

Although in the stepwise regression models the general quality management system, direct regulatory involvement and intrinsic regulatory compliance factors played extremely important roles as determinants of business performance improvements, their existence in the regression equations was more representative than absolute (market share was partly determined by general quality management system scores and by direct regulatory involvement (Equation 1) and profit and sales improvement was partly determined by intrinsic regulatory compliance (Equation 2)) The purpose of stepwise regression is to establish unique representative contributions, however, the roles of the other factors, although only directly and indirectly correlated, were also important The fact that a given company had a good general quality management system and knew the regulations well would not in all

likelihood bring success if that company did not for example make regulatory documentation, such as validation documentation, available to their customers Regulatory documentation provision was correlated significantly to market share Hence the models developed were representative and not mutually exclusive to the factors eliminated by the stepwise model

When considering the regression equations, the independent entries could be considered to be representative of the quality or regulatory cultures within an organisation To get a truer overall picture of the roles of quality and regulatory practices, the correlations plus the regression models needed to be considered In this regard, the factors that were correlated with Market share and Competitiveness which was a non financial measure with financial effects, were general quality management, training and human resource management, use of policies, practices and procedures and the three regulatory factors Sales and profit improvement, a financial measure, was correlated to General QMS and intrinsic regulatory compliance

Software quality, customer service and leadership and design documentation provision were not correlated with any of the business factors but they were all correlated to the general quality management system factor and to most of the regulatory factors, which in turn were correlated to both business performance factors It was not reasonable then to discount the impact of these factors on business performance, in fact as these are co-correlated to some of the same quality

and regulatory practice factors, and they are all indicators of a combined quality / regulatory culture (which are correlated in any case), it can be stated by inference that these were positive contributors to business performance in the pharmaceutical market

Consider again the regression models

Regression Equation 1

Market Share and Competitiveness =

1 932 + 0 353 General QMS + 0 222 Direct Regulatory Involvement + e1

Regression Equation 2

Sales and Profit Improvement =

1 520 + 0 237 Intrinsic Regulatory Compliance + e2

The influences of both quality and regulatory practices were clear There was no doubt that the main predictors of market share and competitiveness and profit and sales improvement were not quality and regulatory performance, but more likely to be related to the product offering, marketing, pricing and competitive strategies of the company However the influence of quality and regulatory practices was significant The influence on Market Share and Competitiveness in the pharmaceutical industry was particularly interesting (R^2 for equation 1 was 20 1%) This was quite a large increase in market share and competitiveness above expectations from employing higher levels of quality and regulatory practices, with General QMS being represented as having the highest unique contribution to the

model The lower R^2 for equation 2 of 4 8% meant that intrinsic regulatory compliance did not have such a large effect on profit and sales improvement, but a 4 8% improvement may be considered to be quite large depending on company expectations

The combined effects that can be seen from both models show two things Firstly that improvements in market share, competitiveness and sales and profits above expectations within the pharmaceutical industry could be achieved through higher levels of quality and regulatory performance and secondly that there was no substitute for the other aspects of business strategy for maximising gain Armitage and Chai [170] and Sadikoglu [171] agree with the assertion that strong financial performance is mainly based on superior competitive practices and internal efficiencies In the case of market share and competitiveness the contribution of quality management alone in the stepwise model (first step) had an adjusted R^2 value of 16 1% So regulatory practices added a further 4% to the total contribution to market share and competitiveness This showed that for this sector that quality practices had the greater effect on business, but that direct regulatory involvement (representing the regulatory effort) was also important

The importance of the regression equations was to establish the strength and direction of relationships and to assess the unique contribution of the set of factors, rather than as a predictive tool It should be therefore viewed qualitatively rather than quantitatively So qualitatively speaking, both quality practices and regulatory

practice had a positive influence on business performance giving support to the study hypotheses H1 and H3 To contrast the case of the pharmaceutical sector against other sectors, this research confirmed that the relationships established between quality and business performance for other sectors were similar to the automated pharmaceutical systems sector as explored later in this section There was however the added aspect of regulatory involvement and compliance and its symbiotic relationship with quality practices, which added a unique contribution to business performance coupled with the indirect mutually beneficial effects on quality practices by regulatory practices, quality practices in turn offering a unique contribution to business performance as determined by the regression models As regulatory practices and quality practices both contribute to an overall quality effort, then the case for the pharmaceutical market of interest must be that it is the entire combined effort of quality practices coupled with regulatory practices that contributes to business success, and that one should not be considered without the other In the case of the regression equation for profit and sales improvement, the independent quality and regulatory practices variables could all be represented by the intrinsic regulatory compliance factor The representation reinforced the fundamental importance of the application of the regulations but once again it was crucial not to ignore the effects of the other mutually beneficial quality and regulatory factors which were inter-correlated as previously described

There has been much work carried out into the relationship between quality practices and business practices in other industries, where regulations were not

considered The research is broadly divided into that which evaluates either quality management or product quality against organisation performance, which may or may not include financial measures Ismail and Hashmi [28] found that companies with lower levels of quality management practices were more susceptible to poor performance than those with higher levels of quality practices for the Irish manufacturing industry In that study market share was used as a performance indicator and the features that made up TQM and ISO9001 quality management were used to form the basis of the independent variable A general index was used for performance and practice scores and a correlation of 0 69 was found between practice and performance The strength of correlation found by Ismail and Hashmi was higher than elsewhere in the literature and 20% higher than the highest correlation found in this study between any quality practice factor and any business performance factor The direction of correlation was positive however and still moderate, which is comparable Lee et al [82] found by using technical measures of quality performance in manufacturing that there was a weak positive relationship between quality and performance, when return on assets and sales growth were used to measure organisational performance There was undoubtedly a difference in the type of measure used here as the focus was on end product quality However the goal of quality management and assurance was end product quality and it was interesting and important to establish that the knock on effects on business performance were also positive The weak positive contribution of product quality was not directly comparable to the findings in this work owing to the difference in measures Forker [80] also established a similar relationship between product and

process quality measures and business performance, whilst looking at the furniture industry

Sharma and Gadenne [30] established that in businesses with top level commitment to quality management programmes, greater emphasis on QM approaches are positively associated with organisation performance, which according to Adam et al [85] is natural and expected Quality management's goal is to eliminate waste and reduce defects Adam et al also recognised the general trend from the literature was of a weak positive influence of quality on financial performance Their use of hard measures of performance such as net profit, return on assets and sales growth, with a combination of quality management and product quality measures yielded a weak positive correlation also Similar to this work, their factor analysis extracted components, which included customers, knowledge, employee involvement and employee satisfaction Hence this research agreed with the work of Adam et al in terms of findings and the representative indicators of quality The preliminary work of Agus [83] into the structural linkages between TQM, product quality performance and business performance in electronics companies which, although it could not confirm structural linkages, did establish correlations that were comparable with this work The independent practices of leadership, customer focus, supplier relations, training, employee focus and quality measurement were all found to have positive correlations to the business performance index which included revenue growth, sales growth, market share and profits as business performance indicators The individual correlations were not stated, just the scale correlations With the exception

of measurement, which was highly correlated, all the correlations were in the low to moderate region

The relationships between quality and business may not be constant over time and caution would need to be exercised when making generalisations from this work Tsekouras et al [84] in a study of 134 Greek firms implementing ISO9000, found that the effects of implementation on business performance may not become clear in the first 5 to 6 years but their evidence suggested that benefits are more long term That study used hard financial performance measures In order to ascertain whether those findings were similar for the pharmaceutical industry, a longitudinal study would be required Adam and Flores [85] showed that the generalisation of the relationship was not always reliable in their comparison of quality practices and financial performance between the US and Mexico It was found that in the US that employee involvement, leadership and emphasis on design and conformance contributed directly to financial performance (return on assets and net profit), whereas the same could not be said for the Mexican case However, not all research concurred with this work Zhang [172] used a dichotomous perceptive measure to establish whether quality practices resulted in improvements in business performance Respondents were asked to answer yes or no to whether increased levels of quality practices resulted in market share increase Only 20% of ISO9000 companies said that market share was increased whereas 60% of TQM companies said that it increased This was possibly as a result of the type of measure employed by the research in that there were no in between options that could assess whether

the sustenance (lack of increase) of market share was deemed to be expected and hence a positive outcome of the heightened quality application, and the singular option was probably not a very effective means of establishing performance This was an exception however as the findings from this work for the automated systems developers in the pharmaceutical industry were generally consistent with the findings from other industries when quality practices and business performance was considered Lemak and Reed [86] for instance also found that an increase in profit margin could be expected after the adoption of TQM practices Therefore in the context of the literature it was deemed that although there is a special case for pharmaceuticals in terms of the added influence of the regulations, the generally established relationship between quality practices and business performance was upheld

5 3 Background considerations and generalisations

The purpose of looking at the background variables was to assess whether the primary relationships established between quality practices and business performance and between regulatory practices and business performance held up under controlled background conditions, to evaluate differences between companies with different characteristics and as a qualification for the generalizations from this research The applicability of the study across the various company sizes, time established in business and in the pharmaceutical industry, regulatory and quality system environments, the complexity of the software used in the respondent's

products and the criticality of those products to the drugs manufactured by their customers were important considerations for this work

When looking at the regulatory groupings it was interesting to find that 91 out of 119 or 76% of respondents developed their systems to FDA guidelines 26 respondents did not know what their regulatory environments were which was unexpected This was probably down to the person responding rather than the organisation not knowing as the vast majority of respondents' websites have references to the FDA in particular Another fact that makes this seem erroneous on behalf of many respondents is that although the question was often answered as unknown, the regulatory questions in the questionnaire were considered and answered Maybe the way the question was asked posed some difficulty although no comments from respondents or from the pilot study indicated this The high number of FDA companies in the study (compared to just 2 for example who claimed to develop to EMEA standards and none who claimed to be from just PIC/S developers) is probably due to several factors Firstly the world pharmaceutical market is heavily dominated by US companies Of the top 20 producers of medicines in 2003, 13 or 65% were American owned [173] and 50% of world consumption is by North America [174] Hence there is a massive requirement for drugs and hence manufacturing systems to be manufactured within, and for, the FDA market Secondly the FDA regulations themselves are more prescriptive, specific and it might be said restrictive, than the EMEA / PIC/S equivalents Compare for example the extensive requirements of the 21 CFR Part 11 rule for electronic signatures with

the closest equivalent in Europe, EU Volume 4 Annex 11 The former is extensive and in its requirements, and better in terms of providing industry with direction for compliance, whereas the latter is more general and shorter Although the actual expectations by regulators may not be much different in either environment in terms of compliance requirements the FDA rules are of a higher standard Part 11 was an FDA response to industry for guidance on the use of electronic record and electronic signature systems No such extensive guidance exists from the European regulators This highlights the general trend of the FDA being world leaders in terms of proscribing requirements for automated / computerised systems used in drug manufacture Hence developers would be shrewd to observe FDA regulations when bringing new products to the market 28 respondents or 23 5% said that they worked to EMEA regulations Therefore sufficient representation existed from this sector, however as only 2 of those respondents did not also work in an FDA environment it was not possible to compare scores between the FDA and the European regulator

The most meaningful analysis that could be done therefore was to look at the data in terms of those companies who operated to FDA regulations only, those who operated in FDA and other environments (including EMEA / PIC/S and ICH), and those who operated in self-proclaimed 'unknown' environments Looking at the regulatory groupings differences were found in terms of software quality and direct regulatory involvement For software control if was found that where respondents gave attention to FDA and at least one other set of regulations that they had significantly higher scores than when just FDA regulations were followed and when

the regulatory environment was unknown It is suggested that the lack of a significant difference in scores between those companies who operated in FDA only environments and those who did not know their regulatory environments may be down to the high range of scores from respondents in the 'unknown' category That is, the lower quartile for the FDA only category only goes as low as 1 6 whereas for the unknown category the range extended below one It is expected that if more accurate answers were achieved for this question then the FDA only category would have resulted in a significantly higher score than the unknown category

What was important to extract from the analysis was that companies with a broader perspective on international regulations scored better in terms of software quality This was perhaps due to a compliance culture that existed in terms of organisations that aim for best practice in software quality being more adept at using and complying with the regulations

In the case of direct regulatory involvement, differences were expected and found between those respondents who knew their regulatory environments and those who did not Both the 'FDA only' and 'FDA and others' categories scored higher than the unknown category If the respondent did not know their environment (as 26 respondents claimed) it is unlikely that they would be adept at complying with the regulations What was noticeable though again was that the FDA and others category scored significantly higher again than for FDA only companies This suggested that an international view of the regulations was more likely to yield better

application of the regulations than just an FDA focus This could be attributable to their greater experience in assessing, applying and complying with varied regulations and implementing quality systems based on the combined knowledge of several sets of regulations However this seemed to be as far as it went with regards to superiority, as there were no significant differences in any of the other factors with respect to regulatory grouping Therefore the actualisation of quality practices such as general QMS or intrinsic regulatory compliance was not significantly different between any of the regulatory sub-groups Whereas no differences were anticipated between the 'FDA only' and 'FDA and others' categories it might be expected that differences would exist between each of these groups and the 'unknown' category However other factors such as the quality management system employed would seem to have played a larger role here

Out of the 119 valid responses, 75 or 63% had ISO registration and no other quality system installed Another 3 respondents had TQM also whilst 7 had only TQM 22 (18 5%) reported having Hybrid systems and 11(9 2%) reported having none Those categories deemed large enough for differential analysis were those companies with ISO only, TQM only, Hybrid systems and no quality systems In total only 10 (8%) of respondents had TQM, which indicates that this quality philosophy was not widely used in this sector The high number of respondents who either had a hybrid quality system or no quality system might in part reflect the industry itself Pharmaceutical companies tend to use proprietary quality systems designed to meet regulatory requirements directly rather than ISO based systems Possibly many of the

developers of automated systems for the pharmaceutical companies follow suit However pharmaceutical companies expect their suppliers to have formal quality management systems and it is normally part of their selection criteria, so having a formal system such as ISO9001 is advantageous Differences were revealed between sub-categories for the two dominant quality implementation factors in the quality and regulatory factor groupings – the general quality management system factor and the intrinsic regulatory compliance factor No differences existed between the ISO only and TQM only categories for either factor In the case of the general QMS factor, both quality system types scored significantly higher than for companies with hybrid or no quality systems As the application of a formal system requires many of the components comprising this factor, then it is reasonable that general QMS scores would be higher for companies with formal systems established The same pattern emerged in the case of intrinsic regulatory compliance with the exception that ISO systems did not score significantly higher than TQM only systems This supports the previously stated possibility that vendors might be adapting hybrid quality systems reflecting those used by pharmaceutical manufacturers focused on regulatory requirements, hence resulting in higher intrinsic compliance scores Companies with hybrid systems scored significantly higher than those with no system in the case of both general QMS and intrinsic regulatory compliance, which again showed the relative superiority of having a formal system not aligned with established systems as opposed to none at all None of the remaining quality or regulatory factors had differentiated scores with respect to the sub-categories examined, demonstrating that the implementation of a formal

system has most effect on the central quality system implementation than on sub-systems that go to make up the greater quality effort

No significant differences were found in terms of business performance between ISO only and TQM only environments Zhang [173] found TQM had better overall effects on business than ISO9000 from a general review of the literature in a pan-sector study It was not clear from that work whether the differences uncovered were statistically significant however The generalisation cannot be extended to this sector though, as regulatory influences would seem to have a greater impact on companies than TQM With regards to quality performance, Sohail and Hoong [95] found that both ISO9000 and TQM practices result in significantly better organisation (and quality) performance, compared to companies without them, which is consistent with this work Ismail and Hashmi [28] found that mean organisation performance was significantly higher for companies with ISO only than for those with TQM only when looking at Irish manufacturing This shows that the implementation of TQM and ISO does not seem to yield similar results across all sectors, and care should be taken when making generalisations

Sohail and Hoong [95] found that there were significant differences in quality performance between those companies operating less than 10 years and those operating more than 10 years Tsekouras et al [84] found that the effectiveness of ISO 9000 quality schemes was not significant in the first 5 to 6 years after adoption This work discovered differences in scores for general QMS, provision of design

documentation, intrinsic regulatory compliance and regulatory documentation depending on the length of time a company was established (and depending on the time they were established in the pharmaceutical industry, which was highly correlated with total time established) In the case of the general quality management system and provision of design documentation scores, those companies established for between 4 1 and 8 years exhibited significantly lower scores than for any other category, including the 0 to 4 years established category It is not understood why this difference existed but possibly very new companies have a very high emphasis on quality management due to newer initiatives such as GAMP 4 and 21 CFR Part 11 and the general direction of quality management, with companies older than 8 years having mature quality systems exposing a gap in the 4 1 to 8 year category It was probably more meaningful to examine the summary categories, which showed that the general QMS score was significantly higher for companies established longer than 16 years than those not established as long There was no significant difference in the provision of design documentation score The difference in general QMS scores was likely to be attributable to maturity in accordance with Crosby [78], Sohail and Hoong [95] and Tsekouras et al [84]

For provision of regulatory documentation a significant difference did exist between those operating less than 16 years and those operating more, so maturity seemed to be a factor here too From the sub-category differential analysis it would seem then that time established did not have significant categorical influence on the other factors in the study which shows for example that software quality, direct regulatory

involvement and business performance scores were not necessarily influenced by time, and that comparable results for these factors were established across the range of time established categories

Sadikoglu [171] found that TQM performance was not dependent on company size This study found differences in scores for general QMS and market share and competitiveness for the questionnaire categories of organisation size, and for general QMS and market share and competitiveness for the corresponding summary categories For general QMS there was a difference between small companies with less than 50 employees and those with greater than 100 No differences were established between the 0-50 employees category and those with between 51 and 100 employees or between those with 51-100 employees and greater than 200, however there was a difference between those with 51-100 and 151-200 No difference existed between those with 101-150, 151-200 or those with greater than 200 Therefore there seemed to be an increase in general QMS scores with organisation size up to a point where it then levelled off With small companies in particular it is often difficult to have individuals dedicated purely to quality and the resources required are often unavailable to fulfil many quality functions As the company sizes increase resources become available and as the complexity of operations increase in sympathy with size companies tend to have dedicated quality staff and more extensive quality systems However it would appear from this study that this is the case up to a company size of 100 employees, beyond which quality systems don't score any higher for this sector

For market share and competitiveness, using the summary organisation size categories, there were significant differences found between small and medium companies, but none between small and large or medium and large companies, so a linear increase was not observed It was hence found that medium sized organisations in this sector tended to have a higher market share than smaller ones, but smaller companies did not have significantly smaller market share and competitiveness improvement scores than large companies Small companies often operate on a niche basis, providing flexible systems and products for their market which can have dramatic effects on market share and competitiveness improvements that might not be as marked in large companies with staple products and services, which have similar size competitors The influence on market share and competitiveness is of course based on many other more complex factors including marketing, new product introductions, competitor practices, product patents and so on so the influence of organisation size should not be overstated

The complexity of the software employed in respondent's products showed significant categorical differences with respect to software control, training and HRM, provision of design documentation, use of procedures, policies and procedures and both direct regulatory involvement and intrinsic regulatory compliance Whilst complexity did not show up any sub-category differences in terms of the main quality management system, many of the related subsystems were very much affected by complexity levels The software control factor showed an upward step change for

each increase in complexity level, therefore controls on software development and maintenance seemed to increase in line with complexity Interestingly, direct regulatory involvement also exhibited the same pattern There are many factors that are likely to influence the software control finding As complexity increases the scope for errors and the difficulty in debugging systems increases, so it makes sound business sense for the developer to employ stringent controls over the development Also, for more complex systems, the number of developers involved is usually greater so that employing a formal means of control can be part of a greater project management effort in terms of avoidance of errors, and coordination of modular activities

For the direct regulatory compliance consideration, more complex systems are likely to be larger systems such as manufacturing control systems, manufacturing execution systems, quality documentation management systems, building management systems, SCADAs, distributed control systems, inventory management systems etc which very often can have considerable impact on product quality Therefore to be competitive in the market, developers need to be in tune with the regulations This is illustrated by GAMP [13], which imposes requirements that increase in line with complexity and risk In the case of intrinsic regulatory compliance a difference in scores was detected between the low and medium complexity categories but no difference was detected between the low and high, or medium and high categories so no pattern of any use emerged

When provision of design documentation was considered differences existed between low and both medium and high complexity levels illustrating that provision of design documentation for low complexity systems would not be seen with the same priority as for higher levels of complexity This was also consistent with the GAMP [13] guidance, which has lesser requirements in this regard for systems with a lower complexity rating For training and HRM and use of procedures, policies and standards there were differences between the low and medium levels of complexity and the high complexity levels For higher levels of complexity it would be expected that the use of standards in particular would increase, particularly when the system in question must be able to interface with other systems The quality expectations in general would also be higher from a regulatory standpoint with regard to procedures and policies used in general for more complex systems, again as required by GAMP [13], but also by the European and US regulations directly [59][70] These requirements also extend to training, which scored higher for the higher level of complexity Thus, from this study it appears that companies operating with differing levels of complexity score differently in terms of quality and regulatory practices

It was important to ensure that the primary relationships were not spurious across the range of possible company backgrounds The stepwise regression results showed that the relationships were upheld when all the background variables were entered into the model, but that criticality of the respondent's product to the drug quality of their customers played a major role when determining business performance From regression equation 3 it was shown that criticality could be used

to represent direct regulatory compliance in the model, showing that this factor had a substantial influence on many of the other quality and regulatory factors in the model That model meant that market share and competitiveness were primarily dependent (amongst the study variables) on the general quality management system and on criticality Also for regression equation 4 where profit and sales improvement was the dependent item, criticality could be used as a factor that determined the improvement in that business factor Hence criticality can be viewed as playing an important part in the extent of direct regulatory involvement and intrinsic regulatory compliance, that is, for the developers developing products for critical use the regulatory practice scores are strongly linked to the criticality Besides the salient role the criticality background variable played with regard to the main relationships established in the study, there were also categorical differences found for general QMS, direct regulatory involvement, intrinsic regulatory compliance, availability of regulatory documentation, market share and competitiveness, and sales and profit improvement This further illustrated the impact that the criticality of the product on customer's drug quality had (see below)

When the summary categories of criticality were assessed for general QMS high levels of criticality scored higher than for medium levels but no difference existed between low and medium or low and high, i e the finding was inconclusive As there were significant increases between low and high, and medium and high scores for the other five differentiated factors the influence of high criticality could be clearly observed High criticality resulted in significantly higher scores for the three

regulatory factors and the two business factors The step increase in regulatory practices is probably attributable to the two way relationship between manufacturers and their suppliers, in that in order to be effective in the market developers must be prepared to meet customer's requirements in terms of compliance, and also that manufacturers demand criticality dependent levels of quality and regulatory practices from their suppliers, that is based on the risk to their processes The business performance scores step increase can be attributed to the selection processes operated by manufacturers, which is based on many things including GMP risk (as outlined in GAMP [13]) That is, many manufacturers will require the quality systems of their suppliers to be of a standard that matches the risk to the product or to their compliance effort, i e the GMP criticality of the automated system Following this, those suppliers with greater regulatory emphasis can expect to have significantly better business performance in the pharmaceutical market than those with lesser emphasis From this work it was clear that developers supplying the higher risk products did in fact have this greater regulatory emphasis and the corresponding knock on benefits in terms of business performance

The benefits from employing hard subjective measures rather than using a direct organizational metrics (such as balanced scorecards [175][176]) approach to assessing business performance proved justified in that a broader picture of the performance of suppliers was possible Without this, analysis of the main Market Share and Competitiveness factor might not have been possible

5 4 Conclusions

The hypotheses of this research were upheld That is, it can be said that high levels of quality practices result in better business performance (H1), that firms with higher general quality implementation levels have a better regulatory focus (H2) and that high levels of regulatory practices results in improved business performance (H3) The relationship between quality practices and business performance for providers of automated systems for use in a pharmaceutical manufacturing environment was consistent with the results found for other sectors, but regulatory factors provided additional business advantages These advantages were particularly marked when the developer was producing systems that posed high risk to the drug product, in terms of in market share and competitiveness, and profit and sales improvements above expectations

The general quality management system employed by a company, and its practices relating to direct regulatory involvement, and actual regulatory compliance had a greater influence than other factors in terms of the improvements in business performance observed Regulatory practices and quality practices are closely related and comprise the overall quality focus in terms of a regulatory market Although there was a very real and positive influence by both regulatory and quality practices on business performance, business performance is primarily determined by other factors related to the developers business and technical practices and the manufacturer's requirements, market niches, product quality etc The symbiotic

relationship between quality and regulatory practices meant that suppliers who adopt regulatory practices are likely to have better quality systems, so that the general quality system and the software quality practices are generally superior for organisations with a regulatory focus

The regulatory environment in which respondents operate has an influence on software quality in particular, and an international regulatory focus tends to result in better software quality practices Broadly similar results were found in this research for TQM and ISO quality systems implementations for the sector of interest This differed from other work, which found differentiated results for these quality systems However, consistent with other work it was found that operating a formal, recognised quality system results in higher levels of quality practices In addition to this, regulatory compliance levels tend to be higher when a recognised quality system is in place Although not as effective as recognised quality systems, hybrid systems were significantly more effective than no quality system at all

The length of time a company is established has an influence on certain elements of quality practices and regulatory practices, particularly the general quality management system where a maturation factor seems to exist Organisation size was also found to have an influence on the general quality management system performance, which increases until companies get larger than 100 employees after which there appears to be no significant change in practices scores

The complexity of the automation of a product influences quality and regulatory practices also, particularly in relation to software quality practices In summary, quality practices, regulatory practices and business performance have a degree of interdependence for developers of automated systems for use by the pharmaceutical manufacturing industry Other important drivers of these three aspects though include complexity of automation and the criticality of the developer's systems to the manufacturer's drug quality Quality and regulatory practices are also determined somewhat by the regulatory focus of a company, the quality system employed, organisation size and the length of time the company has been established

5 5 Recommendations

To maximise business benefits in the pharmaceutical market, developers of automated systems for use in a manufacturing environment should ensure that

1 They have *direct knowledge and implementation of regulatory requirements and guidance*

2 In order to maximise market share and profit and sales improvements that *focus on quality is high*

3 The l*evel of quality and regulatory practices should be matched to the risk* that their systems can pose to the manufacturer's drug quality

4 *The level of quality and regulatory practices should be matched to the complexity of the automation* used in their products

5 The quality and regulatory *emphasis is placed on the general quality management practices* as required by recognised quality standards such as ISO9001 and TQM, *and on effective practices which ensure actual regulatory compliance* Care should be taken to ensure all the other quality and regulatory practices are emphasised also as they are related to the general quality management system and intrinsic regulatory compliance

6 They have *sound knowledge of international regulatory requirements and guidance*

5 6 Limitations of this research and recommendations for further research

This work only considered developers of automated systems, which were operating external to the pharmaceutical manufacturing environment Many automated systems are developed and built by the manufacturers themselves in-house This research did not look into those areas Further to that, it would be a useful body of work to evaluate the relationships between general GMP practices (i e not limited to those concerned with automated systems) for manufacturers and their business performance, however, gathering sufficient data from differing companies might prove difficult It would also be useful to compare the quality and business scores between companies who operated in regulated and non-regulated markets

Another limitation of this work is that the focus was on quality and regulatory systems rather than on the quality of the end product itself Further research would be necessary to establish the relationships that product quality has on business performance, and its relationship to regulatory practices This work looked specifically at pharmaceutical manufacturing There are other areas related to this which were not within the scope of this work which could be included in future research such as the medical devices industry, medical diagnostics and also pharmaceutical clinical trials Furthermore, longitudinal studies could be carried out into how the quality practices, regulatory practices and the relationships with business performance change over time, as regulatory practices in particular change over time in accordance with regulatory 'creep' or 'spiral'

With regards to the methodology employed herein, survey research was carried out as the sole method for acquiring information Supplemental activities could have included direct interviews with respondents in order to confirm the questionnaire findings with face-to-face perceptions Assessment of other indicators of business success such as stock growth or drug manufacturer perceptions might also have been carried out The quality questions used in this research were adapted from variables used in other work It is standard practice in survey research to use questionnaires and questions unaltered from validated instruments It would perhaps have been better to follow this practice for this research, rather than substantially changing the questions to create a new instrument This would have allowed a more complete comparison with other work in the literature than was possible by using a

new set of questions It was felt that the questionnaires available in the literature did not match the requirements of this study, in that they had too many sections that were not relevant It was also difficult to find a complete validated and relevant questionnaire in common usage Therefore, selective adaptation was appropriate

5 7 Thesis Contribution

The contribution made by this thesis includes

1 The creation of a robust and reliable modular survey instrument for assessing any combination of general quality practices, regulatory practices, software quality and perceptive business performance measures for administration by Internet web host, electronic mail or by postal delivery The survey instrument could be applied to in-house pharmaceutical system development, medical device suppliers and clinical trial environments with some small modifications

2 The creation of a methodology for administering electronic surveys based on best practices extracted, evaluated and refined from the existing research on survey analysis achieving substantially higher response rates than achieved in the literature

3 The formulation of a first set of variables derived from themes in the non-academic literature to attempt to evaluate pharmaceutical regulatory practices by bodies external to the industry itself (i e suppliers)

4 The collation of all the regulations pertaining to development of automated systems in the pharmaceutical industry from a European / PIC/S, and US perspective into a single academic body of work

5 A comparison of the interaction between pharmaceutical regulatory practices, software quality practices and general quality practices

6 The creation of a set of principal components analyzed factors for assessing quality practices, regulatory practices and business practices which could be used as a theoretical base for further research

5 8 Research Contribution

The contribution made by this research includes

1 The relationships between quality and business performance in the wider body of literature were compared with the case for the pharmaceutical industry It was found to be generally comparable Pharmaceutical regulatory practices also

played a role as part of the greater quality effort of an organisation, which did not compare to other sectors

2 The first body of research aimed at evaluating the relationships between pharmaceutical regulatory practices and quality practices was performed

3 The first body of research aimed at evaluating the relationships between pharmaceutical regulatory practices and their impact on business performance for those subjected to them was performed

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Appendices

Appendix A 1 Initial e-mail templates

A 1 1 Initial contact mail

Subject Assistance (For the attention of the manager responsible for quality)

Hi there,

Hello to everyone at <COMPANY NAME>

I am looking from some assistance from your Quality manager / Engineering manager I am a PhD student at Dublin City University in Ireland and I am currently carrying out research into the quality and regulatory practices of companies that produce automated/software systems for the Pharmaceutical manufacturing sectors

This involves the collection of data from companies using a simple questionnaire Firstly I need to establish contact with your Quality manager or the person responsible for quality to get agreement to send the questionnaire Your completed questionnaire is completely confidential

Due to the limited number of companies like yourselves, your response is extremely valuable to the study In order to reward respondents I will supply the full results of my research The data and conclusions will show what the best and optimal quality and regulatory practices are for best business performance in the pharmaceutical manufacturing sectors

So if you could forward this mail to your Quality manager it would be really appreciated If your company has several Quality managers within sub-companies, please forward to each Quality manager If you could confirm with me that you have forwarded the mail and who you have contacted this would also be hugely helpful Please do not hesitate to contact me with any questions or concerns

Thanking you in advance,

Diarmuid P Meagher BSc (Hons) MEng MIEI
Department of Mechanical and Manufacturing Engineering,
Dublin City University,
Dublin 9
Ireland

A 1 2 Thank you mail

Subject Thank you

That's fantastic <NAME>

The questionnaire is not difficult, intrusive or time consuming It is currently being validated and I hope to send it out in the next six weeks Every respondent I get is worth their weight in gold to me

Thanks again,
Diarmuid

Appendix A 2 Non- response e-mail templates

A 2 1 No response mail

Subject Product Quality
Hi,
I contacted <COMPANY NAME> a few weeks ago looking for information from the person responsible for the quality of your end-products I received no response The Quality Manager or Engineering Manager would probably be able to provide me with the information I need I would be obliged if you could pass this mail on to someone relevant or maybe if you could provide me with a more appropriate e-mail address to use

Thanking you,
Diarmuid Meagher

A 2 2 Response to answered 'no-response mails'

Subject Re Product Quality

Hi <NAME>,

Thank you for your prompt response I am a PhD student in Ireland (Dublin City University) and I am researching the quality aspects of the manufacture of systems and equipment used in Pharmaceuticals I have a survey questionnaire that is not in any way intrusive and easy to complete which asks about your quality system and regulatory awareness

I am currently in the process of gathering together a list of companies like <COMPANY NAME> who are willing to participate It is completely confidential and the findings will be made available to your company which may have business advantages Is there any way you can help? It would really be hugely appreciated

Regards,
Diarmuid

Appendix A 3 Pre-test instructions

Pre test instructions

Your assistance with pre-testing my questionnaire is massively appreciated Below you will see instructions for the pre-test Please feel free to comment on any aspects of the pre-test, the instructions for completing the questionnaire, and the questionnaire itself
The purpose of the questionnaire is to gather data relating to 1) Quality practices, 2) Regulatory Practices and 3) Business Performance for manufacturers of automated / software systems for use in all areas of pharmaceutical manufacturing

Data relating to the study variables will be collected as well as data for some background variables as seen in appendix 1 to these pre-test instructions

Instructions

1 Please complete the questionnaire as it is according to the Questionnaire Completion Instructions Place as many comments on the questionnaire as you like
2 Suggest any additions to the questionnaire
3 Discuss aspects of the existing questionnaire that might need to be changed
4 Suggest any changes to the completion instructions and the method of administration

Please indicate how you felt about the following aspects of the questionnaire (You can just type below the following questions if you like)

a) Was it simple to understand?
b) Was it clear?
c) Was it difficult to answer?
d) Was it ambiguous?
e) Were the questions specific enough?
f) Did the questionnaire take too long to complete?
g) Were the concepts mentioned commonly known in your opinion? Should there be more background information?
h) Did the questions adequately relate to the variables in appendix 1 in your opinion?
i) How did you feel about answering the business performance questions?

Please collate your comments and return a copy of the completed and annotated questionnaire when you are ready
Again, thank you so much
Diarmuid

Appendix 1(to pre-test instructions) **Study and Background Variables**

Study variables

QUALITY

22 Training and development
23 Cost of quality
24 Customer focus and feedback
25 Quality system infrastructure
26 Leadership
27 Communication
28 Quality planning
29 Supplier Management
30 Software lifecycle approach
31 Measurement
32 Documented quality policies and responsibilities
33 Use of standards, practices and procedures
34 Requirements management and evaluation
35 Reviews and audits
36 Software control
37 Testing management
38 Teamwork, human resource management and employee involvement motivation
39 Quality driven documented processes
40 Preparation for delivery / approval for release and product realization
41 Service provision
42 Risk management

REGULATORY

1 Extent of use of the GAMP guidelines
2 Extent to which validation features are designed into products
3 Extent to which other regulatory requirements are designed into the software
4 Extent of direct use of GMPs in design
5 Extent of regulatory training for system developers
6 Knowledge and application of rules for electronic records and electronic signatures
7 Availability of source code to manufacturers
8 Extent of provision of design documentation
9 Extent of provision of validation documentation
10 Extent of planning of regulatory activities into design
11 Extent of regulatory design reviews

BUSINESS PERFORMANCE

1 Market Share
2 Growth in market share
3 Net profit as a percent of sales
4 Profit growth
5 Sales growth
6 Average past 3 years sales growth
7 Order book growth
8 Workforce growth
9 Increase in product range
10 Percent sales from new products

Background variables

12 Length of time in business
13 Length of time serving pharmaceutical industry
14 Company size
15 Complexity of automation used in products
16 Regulatory environments
17 End price trends due to regulatory changes
18 End price trends due to quality changes
19 Criticality of product to drug quality
20 Applicability of company quality system to development environment
21 Organisation type
22 Quality system independence from client
23 Quality management environment

Appendix B 1 The survey questionnaire

(The formatting here does not match the formatting of the actual questionnaire document exactly due to page set-up differences)

Survey of quality practices, regulatory practices and business performance for developers of automated systems for use in pharmaceutical manufacturing

This questionnaire is part of a study into the relationships between business performance and quality practices / regulatory practices for developers of automated systems into the life science and pharmaceutical manufacturing industries Due to the relatively limited amount of suppliers to the pharmaceutical industry a high response rate is imperative, therefore your responses are extremely valuable

Please answer all the questions below in full Some of your answers may require input from other departments Your responses are **completely confidential** and the findings of the study will be made available to all respondents who request them

Please feel free to make as many comments as you like to clarify your answers

Section I Background questions

In each case put an 'x' in the box that best represents you and your company.

1 How long has your company been established?

0 to 4 years	4 1 to 8 years	8 1 to 12 years	12 1 to 16 years	>16years
[ ]	[ ]	[ ]	[ ]	[ ]

2 How long have your company been supplying pharmaceutical manufacturers?

0 to 4 years	4 1 to 8 years	8 1 to 12 years	12 1 to 16 years	>16years
[ ]	[ ]	[ ]	[ ]	[ ]

3. How many people are employed within your organisation?

0-50	51-100	101-150	151-200	>200
[ ]	[ ]	[ ]	[ ]	[ ]

4. How would you rate the maximum complexity of the automation/software that makes up your end products?

Not very complex (i e development time takes or took of a few months) ... Very complex automation/ software (i e development time takes or took many months/years)

0	1	2	3	4	5	6
[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]

5 For which regulatory manufacturing environments do you produce automated systems (put an 'x' in each box that applies)?

EMEA	FDA	PIC/S	ICH	WHO	Not Known
[ ]	[ ]	[ ]	[ ]	[ ]	[ ]

Other(s) _____

6. To what extent do customers look for a quality plan from your company?

Never [ ] Rarely [ ] Often [ ] Very Often [ ] Always [ ]

7. What percentage of your clients would you say carry out audits of your quality system?

0-20%	21-40%	41-60%	61-80%	81-100%
[ ]	[ ]	[ ]	[ ]	[ ]

8. How critical would you say that your most critical product is to the quality of the drugs produced by your customers?

Not at all critical			Fairly critical			Highly critical to drug quality
0	1	2	3	4	5	6
[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]

9. Which describes your company best:

Pre-develops products away from the drug manufacturer's site [ ]A
Production facility engineering (Design / Build / Validation) [ ]B
Other: _____

10. *(Only answer if B is selected above).*
To what extent are your quality systems independent from the quality system used by your clients?

Clients quality system used completely [ ]
Mostly the client's quality system is used [ ]
Mostly our quality system is used [ ]
Our own quality system is used alone [ ]

11. What is your company's quality management environment? (Select all that apply)

ISO [ ] ( ) TQM [ ] CMM [ ] Six Sigma [ ] Hybrid [ ]
(state which ISO(s))
Other(s): _____

12. What formal engineering or software standards do you use (please list)? None [ ]
: _____

Section II: Organizational Management

The following section describes specific organizational management characteristics.

Please indicate the extent of your organisations adherence to those characteristics by placing an 'x' in the box below on the scale of 0 to 4, where: **4 = To a very great extent, 3 = To a great extent, 2 = To some extent, 1 = To a very little extent, 0 = Not at all.**

Please answer honestly and remember that all data is completely confidential.

To what extent do you agree it can be said of your company that:

	0	1	2	3	4
13. Staff receive *thorough* training for their job functions					
14. There is a high emphasis on personal development of staff.					
15. Leaders reinforce a culture of excellence.					

16. Employees in general are heavily empowered.					
17. Employees feel valued, recognized and rewarded.					
18. Employees have formal goals and objectives.					

Section III: Quality Management Systems

The following section describes specific regulatory quality management characteristics.

Please indicate the extent of your organisations adherence to those characteristics by placing an 'x' in the box below on the scale of 0 to 4, where: **4 = To a very great extent, 3 = To a great extent, 2 = To some extent, 1 = To a very little extent, 0 = Not at all.**

Please answer honestly and remember that all data is completely confidential.

To what extent do you agree it can be said of your company that:

	0	1	2	3	4
19. Regular training is provided in quality techniques.					
20. Customers rate our customer service very highly.					
21. Customers are involved in the improvement of systems, products and procedures.					
22. Customer relationships are well managed and nurtured					
	0	1	2	3	4
23. Senior management are involved in decision making processes related to quality.					
24. Quality issues are reported to top management.					
25. Management are very committed to improving quality					
26. Management have excellent interaction with customers.					
27. The quality system is well known throughout the company.					
28. Issues, problems and changes are communicated very quickly within the company.					
29. Quality issues are regularly discussed at meetings.					
30. Quality is very well planned.					
31. The company is very knowledgeable of its supplier's quality management practices.					
32. Quality policies are well known by staff.					
33. The quality policies are widely available.					
34. People work very closely to pre-scribed procedures.					
35. People work very closely to industry standards.					
36. Product requirements are evaluated against specifications *during design projects.*					
37. Product requirements are evaluated against specifications *before project close out.*					
38. Reviews of the quality system are regularly carried out.					
39. Reviews of general work practices are regularly carried out.					
40. Compliance audits are regularly carried out.					
41. Information is extensively gathered and retained during *product design –develop – build phases*					
42. Information is extensively gathered and retained during *product testing.*					
43. Supplier performance is measured.					

44	Performance indicators are used as a key driver for change					
45	Day to day work practices are thoroughly documented					
46	Direct after sales technical service is available to customers					
47	Third party after sales technical service is available to customers					

48. It can be said of your customer complaints system that it:

Doesn't really exist [ ]
Is informal [ ]
Is formal but not that developed [ ]
Formal system, well developed [ ]

49 What percentage of your company's time in design, development, build and testing phases would you say is spent carrying out documentation?

0-20%	21-40%	41-60%	61-80%	81-100%
[ ]	[ ]	[ ]	[ ]	[ ]

50 It can be said of your company that customer satisfaction surveys

Are never performed [ ]
Are rarely performed [ ]
Are often performed [ ]
Are very often performed [ ]
Are extensively performed [ ]

51. It can be said of your quality management system that:

No one in particular is responsible for quality [ ]
There are many people responsible for quality [ ]
There is one person responsible for quality (not a Quality Manager) [ ]
There is someone working part time as a Quality Manager [ ]
There is at least one dedicated full time quality manager [ ]

52. Which would you say applies to your company (Place an 'x' in each box that applies)

Quality is a purely a manufacturing /engineering responsibility [ ]
The company has a strong quality leader who works as part of Engineering/manufacturing [ ]
The quality department reports to top management, where the Quality Manager has a role in company management [ ]
The Quality Manager is a senior person in your company and gets directly involved with customers [ ]
There is a Quality Manager on the board of directors Quality is a major 'thought leader' [ ]

53 It can be said of your company that quality awareness campaigns are run

Never [ ]
Rarely [ ]
Often [ ]
Very Often [ ]

54. It can be said of your company that established multi-departmental teams.

Do not exist [ ]
Exist but rarely meet [ ]
Exist and often meet [ ]
Exist, meet often and are effective [ ]

55 It can be said of your company that a quality plan stating *future* objectives:

Does not exist	[ ]
Exists but is not really adhered to	[ ]
Exists and is mainly adhered to	[ ]
Exists and is completely adhered to	[ ]

56. It can be said of your company that quality agreements with main suppliers:

Are not in place	[ ]
Are maintained informally	[ ]
Are formally maintained for some main suppliers	[ ]
Are formally maintained for all main suppliers	[ ]
Not Applicable	[ ]

57. It can be said of your company that supplier audits are carried out:

Never	[ ]
Rarely	[ ]
Often (randomly)	[ ]
Routinely	[ ]
Not Applicable	[ ]

58. It can be said of your company that for internal performance measurement:

No system exists	[ ]
An informal system exists	[ ]
A formal system exists which is not always up to date and accurate	[ ]
A formal up to date and accurate system exists	[ ]

Section IV. Regulatory related practices

The following section describes specific regulatory practice characteristics Please indicate the extent of your organisations adherence to those characteristics by placing an 'x' in the box below on the scale of 0 to 4, where **4 = To a very great extent, 3 = To a great extent, 2 = To some extent, 1 = To a very little extent, 0 = Not at all**

To what extent do you agree that it can be said of your company that

	0	1	2	3	4
59 System developers are knowledgeable of GMP					
60 Design work is well documented whether or not a customer requests it					
61 GAMP guidelines are used					
62 The GMP regulations are a major design consideration for your company's products					
63 *System designers and developers* receive regulatory compliance training					

64 To what extent does your company use GAMP rather than other industry standards

Mostly industry standards used			Used equally				Mostly GAMP used
0	1	2	3	4	5	6	**Neither used**
[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	[ ]	**[ ]**

65 Features are *built into* your products to aid validation

Not really at all	[ ]
Few Features	[ ]
Many features	[ ]
Extensively	[ ]

66. Validation is considered as early as product design

Not really at all	[ ]
Rarely	[ ]
Usually	[ ]
Always	[ ]

67 The Quality Management System is based on regulatory requirements

Regulatory requirements not really considered in system structure	[ ]
Regulatory requirements considered in a small way in system structure	[ ]
Many elements of system structure based on regulatory requirements	[ ]
The system was built to ensure complete regulatory compliance	[ ]

68 Design documentation for your company's products

Does not really exist	[ ]
Exists but is not available to customers	[ ]
Exists and is made available to customers as a standard package	[ ]
Exists and is tailored to meet customer requirements	[ ]

69 Validation documentation for your company's products:

Does not really exist	[ ]
Exists but is not available to customers	[ ]
Exists and is made available to customers as a standard package	[ ]
Exists and is tailored to meet customer requirements	[ ]

70 Regulatory compliance audits of all your products and systems are carried out

Never	[ ]
Rarely	[ ]
Often	[ ]
Very often and randomly	[ ]
Often and routinely	[ ]

Section V Software quality related practices

(RELEVANT TO ALL COMPANIES THAT HAVE CODE PRESENT IN PRODUCTS IN ANY FORM e g. PLC code, software, firmware, SCADAs etc)

The following section describes specific software quality related practice characteristics Please indicate the extent of your company's adherence to those characteristics by placing an 'x' in the box below on the scale of 0 to 4, where **4 = To a very great extent, 3 = To a great extent, 2 = To some extent, 1 = To a very little extent, 0 = Not at all**

To what extent do *you* agree it can be said of your company that

	0	1	2	3	4
71 Security of code is managed during development					
72 There is a high knowledge of 21 CFR Part 11					

73 Training is provided on 21 CFR Part 11 related matters

Not at all	[ ]
Rarely	[ ]
Often	[ ]
Very Often	[ ]
Extensively	[ ]

74 How would you categorise the process under which firmware/software is/has been developed for your company

No real life-cycle model used	[ ]
Informal life-cycle model used	[ ]
Formal *in-house* life-cycle model used	[ ]
Formal *recognised* life-cycle model used	[ ]

75 Your company's system for revision control of software·

Does not really exist	[ ]
Exists informally	[ ]
Is formal and fairly effective	[ ]
Is formal and very effective	[ ]

76 Products and systems are *designed* to be compliant to standards for.

		Not really	Not needed	Partly	By practice	By design
A	Electronic records?					
B	Electronic signatures?					
C	Audit Trail?					
D	Privacy of the individual citizen?					
E	Security?					

77 Source code is made available to drug manufacturers·

Not at all	[ ]
In very limited circumstances	[ ]
Where required using 3rd party agreements	[ ]
Where required using direct agreements with clients	[ ]

Section VI Business performance

The purpose of the section is to get an overall view of your organisations business performance It may require input from other departments Please provide as much information as possible and **provide your closest estimate to the following questions**

78 What percentage of your annual revenue is derived from sales to the pharmaceutical industry?

0-20%	21-40%	41-60%	61-80%	81-100%
[ ]	[ ]	[ ]	[ ]	[ ]

79. During the past 5 years, your market-share in the pharmaceutical industry

Has reduced significantly	[ ]
Has reduced by a small amount	[ ]
Has remained the same	[ ]
Has increased by a small amount	[ ]
Has increased significantly	[ ]

80 For your products that are sold into the pharmaceutical industry overall profit levels for the last 5 years have

Been considerably below expectations	[ ]
Been below expectations	[ ]
Met expectations	[ ]
Exceeded expectations	[ ]
Greatly exceeded expectation	[ ]

81 For your products that are sold into the pharmaceutical industry sales volumes for the last 5 years have

Been considerably below expectations	[ ]
Been below expectations	[ ]
Met expectations	[ ]
Exceeded expectations	[ ]
Greatly exceeded expectation	[ ]

82. For your products that are sold into the pharmaceutical industry percentage sales from new products in the last two years have

Been considerably below expectations	[ ]
Been below expectations	[ ]
Met expectations	[ ]
Exceeded expectations	[ ]
Greatly exceeded expectation	[ ]

For products sold into the pharmaceutical industry, indicate your company's performance in relation to competitors in terms of.

83	Market Share	Low0 1 2 3 4 5 6High [ ][ ][ ][ ][ ][ ][ ]
84	Overall competitive position	Low0 1 2 3 4 5 6High [ ][ ][ ][ ][ ][ ][ ]

Thank you for your valued time The value of your contribution to this study cannot be underestimated

PLEASE SAVE THIS COMPLETED QUESTIONNAIRE AND RETURN BY E-MAIL TO diarmuid.meagher3@mail.dcu.ie or alternatively please post by normal mail to

Diarmuid Meagher,
12 Foxpark,
Finnstown Abbey,
Lucan,
Co Dublin
Republic of Ireland

or

Diarmuid Meagher,
c/o Professor M S J Hashmi,
Dept of Mechanical and Manufacturing Engineering,
Dublin City University,
Dublin 9
Republic of Ireland

Please feel free to comment as desired on any aspects of the questionnaire

Appendix B 2 Questionnaire instructions

Instructions

Please answer the questionnaire for your software / automated system development environment as best you can

There are 3 easy ways to complete the questionnaire

1 Online using the secure online questionnaire
https //fs19 formsite com/diarmuid/Diarmuid/secure_index html
(You can save your questionnaire and return to it at any time if you have to leave it for any reason)
2 Use the attached MS Word questionnaire This can be completed on your PC and returned by e-mail For this just save the document under whatever name you wish, complete and return to diarmuid meagher3@mail dcu ie
3 Alternatively you can print the questionnaire, complete it by hand and return it by post to the address on the end of the questionnaire

If you wish to identify yourself on the questionnaire you can, but this is completely up to you It would be appreciated though if you are using the online questionnaire or returning the questionnaire by post that you inform me by e-mail that you have completed a questionnaire

Again, thank you very much for your invaluable assistance Results of the study will be made available to all participants

STATEMENT OF CONFIDENTIALITY, ANONYMITY AND NON-DISCLOSURE
Any data or information supplied through the questionnaire answers or by e-mail is completely confidential and will not be disclosed to any parties within or external to Dublin City University No e-mails or respondent details will be disclosed to third parties Any further assurances required are available on request in whatever way required by respondents Once the data from questionnaires is entered onto the study database it will no longer be possible to link respondents to their supplied data E-mails will be destroyed securely

Appendix C 1 Reliability analysis for pilot study data (N=29)

Only variables with two or more associated questionnaire items were considered for this analysis The items dropped for the purpose of reliable pilot analysis were not necessarily dropped for the main study data Some of the sub-variables used to make up the pilot study main variables are not considered below as they only have one questionnaire item associated with them, meaning that no analysis was necessary

Variable	Items	Cronbach's Alpha	Items Removed	Revised Alpha	Justification
Training and Development	13 14 19	0 712			
Teamwork and HR	16,17 18	0 795			
Customer focus	48, 50, 20, 21, 22	0 702			
Leadership	15, 23, 24, 25 26	0 729			
Communication	53, 54, 27 28, 29	0 469	53,54	0 663	Removed items 53 and 54 to allow a reliable representation of Communication using the three Likert scaled items 27 to 29 The three remaining items focused directly on the variable The 'tools' questions were dropped
Quality Planning	30, 55	0 333	55	1	As these items did not vary together, the quality planning variable was assessed through the single item which assessed directly whether quality was planned well
Documented quality practices	32, 33	0 687			
Use of standards, practices and procedures	34 35	0 808			
Requirements Management	36 37	0 849			
Reviews and Audits	38 39, 40	0 699			
Quality driven documented processes	41 42,45,49	0 732			

Variable	Items	Cronbach's Alpha	Items Removed	Revised Alpha	Justification
Measurement	44, 58	0 434	44	1	Question 44 removed (how performance indicators are used) Single question used to assess extent of measurement
Quality system infrastructure	11a-e, 51, 52	0 185	51	0 548	Reliability far from ideal for this variable Corrected to 0 548 by omitting item 51, which asked about QMS responsibility Variable represented by presence of a QMS and maturity of QMS
Supplier management	31, 43, 56, 57	0 609			
Extent of use of GMPs	59, 62 63, 67	0 882			
Extent of provision of design documentation	60 68	0 435	60	1	The single question regarding availability of design documentation was asked This question directly represented the variable
Extent of use of GAMP	61 64	0 824			
Extent to which validation features are designed into products	65, 66	0 755			
Software control	71, 75	0 893			
Knowledge and application of rules for electronic records and signatures	72 73 76	0 878 (0 899 for scale making up question 76)			
Competitive strength relative to competitors	83, 84	0 94			

Appendix D – Collated quality practices criteria

Quality criteria	Source1	Source 2	Source3	Source4	Source5	Source6	Source7	Source8	Source9	Source10
Average percent items defective	Adam et al									
Cost of quality	Adam et al	Crosby								
Customer focus and satisfaction	Adam et al	Yee Tsang	Rao	McAdam	Parzinger	MBNQA	ISO	EQA		
Teamwork, human resource management and employee involvement / motivation	Yee Tsang	Rao	McAdam	EQA	Parzinger	MBNQA	ISO			
Continuous quality improvement	Yee Tsang	EQA	Parzinger	MBNQA	ISO	Crosby				
Top management leadership, commitment and recognition of quality	Yee Tsang	Radding	Rao	McAdam	EQA	Parzinger	MBNQA	ISO	CMM	Crosby
Training and employee development	Yee Tsang	McAdam	EQA	Parzinger	ISO	CMM	IEEE 730	Rao	MBNQA	

Quality criteria	Source1	Source 2	Source3	Source4	Source5	Source6	Source7	Source8	Source9	Source10
Sound quality system infrastructure	Yee Tsang	Rao	EQA	CMM	Crosby	ISO	MBNQA	Radding		
The role of supervisory leadership	Yee Tsang	EQA	MBNQA							
Communication within the company	Yee Tsang	EQA	ISO	CMM	Crosby	MBNQA				
Supplier partnership and supplier management	Yee Tsang	Rao	McAdam	EQA	MBNQA	ISO	IEEE 730			
Measurement and feedback	Yee Tsang	Radding	Rao	EQA	Parzinger	MBNQA	ISO	CMM	Crosby	McAdam
Cultural change	Yee Tsang	Crosby								
Creation of a common quality language	Radding									
Quality as a design function	Radding									
Building testability into development	Radding									
Automated software quality products	Radding									

Quality criteria	Source1	Source 2	Source3	Source4	Source5	Source6	Source7	Source8	Source9	Source10
Strategic quality planning	Rao	McAdam	EQA	MBNQA	ISO	IEEE 12207.0				
Explicit organizationally linked policies	Rubey	McAdam	EQA	ISO	IEEE 730					
Quality assurance plans	Rubey	IEEE 12207.0	IEEE 730	Rao	MBNQA	ISO				
Use of standards, practices, procedures and conventions	Rubey	IEEE 12207.0	IEEE 730	ISO						
Requirements evaluation	Rubey	ISO	CMM	IEEE 12207.0	IEEE 730					
Design evaluation	Rubey	ISO	IEEE 730							
Test evaluation	Rubey	ISO	IEEE 730	Radding						
Reviews and audits	Rubey	ISO	CMM	IEEE 730	MBNQA					
Evaluation of software development processes	Rubey	ISO								
Software library control	Rubey	ISO								
Configuration management	Rubey	CMM	IEEE 12207.0	IEEE 730	ISO					
Subcontractor control	Rubey	CMM								

Quality criteria	Source1	Source 2	Source3	Source4	Source5	Source6	Source7	Source8	Source9	Source10
Non-developmental, non-deliverable and customer supplied items evaluation	Rubey									
Problem reporting and corrective action	Rubey	ISO	Crosby	IEEE 12207.0	IEEE 730					
Preparation for delivery / approval for release and product realization	Rubey	ISO								
Quality records	Rubey	ISO								
Audit of SQA	Rubey	ISO								
Stated rights and responsibilities of customer and contracting organization	Rubey									
Obtain data about customers	McAdam	MBNQA	ISO	EQA						

Quality criteria	Source1	Source 2	Source3	Source4	Source5	Source6	Source7	Source8	Source9	Source10
Formation of short term problem solving teams	McAdam									
Documented and systematic processes	McAdam	EQA	MBNQA	ISO	CMM	IEEE 12207 0	Crosby	Parzinger	Radding	
Information and knowledge management	EQA	MBNQA								
Financial, building and equipment management	EQA	ISO								
Use of quality tools	Parzinger	IEEE 730								
Cycle time reduction	Parzinger									
Customer feedback driven improvement	Parzinger	EQA	MBNQA	Rao	ISO					
Organizational and personal learning	MBNQA	McAdam								
Capacity for rapid change and flexibility	MBNQA									
Focus on the future	MBNQA	EQA								

Quality criteria	Source1	Source 2	Source3	Source4	Source5	Source6	Source7	Source8	Source9	Source10
Managing for innovation	MBNQA									
Social responsibility	MBNQA									
Quality manual	ISO									
Defined roles and responsibilities	ISO									
Management review of processes	ISO	MBNQA								
Infrastructure	ISO									
Change management and control	ISO	CMM	IEEE 730							
Service provision	ISO	IEEE 12207.0								
Project management tracking and oversight	CMM									
Requirements management	CMM	ISO								
Defect prevention	CMM	Crosby	Parzinger							
Lifecycle approach	IEEE 12207.0	IEEE 730	ISO							
Validation and testing plans	IEEE 730	ISO								

Quality criteria	Source1	Source 2	Source3	Source4	Source5	Source6	Source7	Source8	Source9	Source10
Risk management	IEEE 730	ISO								