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THE VALIDATION OF PHARMACEUTICAL BUILDINGS

By

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A thesis submitted as partial fulfilment of the requirements for the degree of

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VOLUME ONE

ABSTRACT

The construction, commissioning and hand-over of pharmaceutical manufacturing buildings have become increasingly controlled by the requirements of regulatory agencies. Legislation requires that the process of *validation* is undertaken to establish that the facility is constructed in-line with the principles of pharmaceutical *Good Manufacturing Practice* (GMP).

The validation process acts to ensure that the construction and building services systems are designed, installed and operate as intended and do not affect the quality of the manufactured product.

A central objective of this thesis is to examine the sequential validation process and influencing factors that contribute to the facility attaining agency approval.

A comprehensive review of the available literature indicates that projects regularly fail to meet their regulatory objectives due to the building provider and client's differing understanding and views of the validation process and of GMP.

From this literature a validation model is derived and proposes that the design, installation and operation stages of the validation activity are time-series dependant sub-processes controlled through sensing, feedback and comparison.

The research was largely qualitative, case-study based and used an interpretivist approach to analysis, which relied on participant observation and grounded theory techniques. Additional, external validation of the model was sought by collecting and analysing empirical data from an industry questionnaire.

The results of the study demonstrate that significant deviations between the model and the data exist and measures to construct compliant pharmaceutical buildings are often underdeveloped and result in unsuccessful project outcomes.

The criteria by which the success of any construction project is judged are normally time, cost and quality. Time and cost are readily measurable, but the meaning of quality, in relation to the validation activity, can be more elusive and this is at the root of the problem of successful validation of pharmaceutical buildings.

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Finally, I would like to dedicate this research work to the memory of Rita Mary Render (1939 – 1998).

Chapter One: Introduction

1.1 Introduction – Current Knowledge and Need for the Study

The pharmaceutical industry employs around 83,000 people in the United Kingdom (UK) and the sector contributes £2.5 billion annually to British Gross Domestic Product (GDP) (The Association of the British Pharmaceutical Industry (ABPI), 2005).The industry is one of Britain's leading manufacturing sectors, and generated a trade surplus of £3.4 billion in 2004. Analysis reported by ABPI, 2005 of the world's top 100 medicines reveals that, after the USA, Britain's pharmaceutical companies' market share is greater than all its European competitors combined.

Research and development is central to the pharmaceutical industry and it invests 30% of its sales in research, amounting in expenditure in the UK of more than £3 billion i.e. more than £10 million a day. (Ernst & Young's Global Pharmaceutical Report, Ernst & Young, 2004). Over the last 10 years, within the UK economy, pharmaceutical products have constantly been in the top three industrial sectors in terms of trade surplus (ABPI, 2005).

Pharmaceutical products are the subject of government controls and intensive competition. The control of medicines in the UK is primarily through the system of licensing and conditional exemptions from licensing laid down in EC legislation, the Medicines Act 1968 and in relevant subordinate legislation (Medicines and Healthcare products Regulatory Agency (MHRA), (2005). The Licensing Authority also monitors the safety of licensed drug products, through audits, and takes appropriate actions when product is adversely affected. The legislation also covers the premises and requires that the facility be located, designed, constructed and maintained to suit its future operations.

The UK construction industry designs, constructs and maintains process plants across the UK and has a major impact on the UK economy, directly contributing around 1.5% of GDP and employing around 50,000 people (Engineering Construction Industry Training Board (ECITB), 2005). The importance of constructing pharmaceutical facilities which comply with current Good

Manufacturing Practice (GMP) is critical as the construction industry underpins the UK production of crucial products such as medical devices and healthcare products. It is therefore essential in a pharmaceutical facility construction project that the resultant facility is shown to perform satisfactorily and to current quality assurance regulations. The way in which this is demonstrated is by implementing a process of documentation and system testing known as validation.

Due to the nature of pharmaceutical manufactured goods it is important that the facility functions effectively and does not adversely affect the product in any way. According to Begg (1997, p.9), the term pharmaceutical validation became common in the mid 1970's, originating in the USA and reaching Europe several years later. A methodical process of test protocols for validation was developed. In time protocols termed Design Qualification (DQ), Installation Qualification (IQ), Operation Qualification (OQ), Process Qualification (PQ) were written and followed.

It has been widely reported in the pharmaceutical trade press and it is the experience of the writer that construction projects of this type fail to meet their initial validation objectives. In light of the reported process failures and lack of empirical research knowledge, this study asks why these failures occur and how might the process be improved.

1.2 Current State of Knowledge

The literature covering the validation of pharmaceutical facilities comes from the pharmaceutical sector and is largely based on practitioner's experiences and not on empirical research studies.

Trade journal literature within the pharmaceutical sector is the most common form of literary commentary and consistently reports of increasing validation costs (Bender, 1996), problems of interpreting legislation (Wood, 2001) and unsuccessful regulatory outcomes (Dream, 1994). Research studies are uncommon and either relate to computer systems or manufacturing process validation.

The commonly reported unsuccessful outcomes often are related to specific implementation themes and include planning (James, 1998), complexity (Wingate, 1997), project change (Gorges, 1981), regulatory understanding (Tashijan, 2000, James, 1998, Allan, 2004), embedded errors (Roper, 1994; Render *et al*, 2005), sequencing (Wheeler, 1994) and project termination (Meredith & Mantel, 2000).

James (1998, p.74) notes that it is acknowledged within the industry that validation is required. However, the quantity and time required to implement are not well understood thus resulting in an inaccurate planning process.

Wingate (1997, p.7) suggests that the increase in complexity of automated equipment, such as that used in pharmaceutical manufacturing processes, has increased significantly. The effect of this increased technological complexity is to increase the level of potential problems related to testing the facility to ensure the health and safety of the drug product user. Wingate (1997) also notes that with increased complexity comes the regulatory expectation of the adoption of an adequate validation system.

Commentators such as Tashijan, 2000, James, 1998 and Allan 2004 argue that GMP regulations are general or vague, adopt unfamiliar terminology and have obscure roots and logic which serve to hinder the understanding of those charged with the task of implementation.
An industry that has many parallels with that of facility validation is computer software testing. In the same way that the pharmaceutical product is critical and requires life-cycle testing, a great number of computer software applications require a high degree of system testing and validation takes place where the project outcome is critical in nature.

Roper (1994), a commentator on the software testing industry, discusses the concept of embedded errors which can often manifest themselves later in the project as faults and finally, failure. The same is also true of errors within the validation process, typically as a result of inadequate testing, which can result in post-project failure demonstrated through regulatory inspection non-compliances.

Wheeler (1994, p.48) notes the importance of sequencing the commissioning and validation activities on facility start-up and compliance. The disadvantage of not considering both activities in parallel can result in wasteful duplication of tasks. Meredith & Mantel, (2000, p.541) underline the importance of the final stages of the validation process. The project termination phase is of particular significance to project success and the adoption of an integrated approach between building provider and user is vital in achieving an environment which allows the client to satisfy his operational and governing GMP requirements.

In most cases the literature lacks completeness, rigour and balance and is almost unknown outside the sector environment. The significance of this is that there is a clear need to provide more in-depth, balanced research to add to the limited commentary provided by only those mainly involved in the pharmaceutical sector so as to allow those in the construction sector to share and use this information. Quality and Total Quality Management (TQM) have been debated at length in recent years by construction industry commentators (Egan, 1998, McCabe, 1998 & 2001). Construction sector searches for validation related literature have demonstrated that there is little or no discussion on the subject of facility validation.

1.3 The Need for the Study

In light of the above mentioned literature there is a clear need for the study because:-

1. A distinctive research study of this type which models the validation process based on applying systems analysis to explain the problem, will increase understanding of the complex validation process. As will be explained in chapter two and three, the formation of the project environment and impact on the process implementation will be influenced by modelling the relationships of both the construction and pharmaceutical sectors.

2. Only specific individual topics have been reported in pharmaceutical industry papers and these have not been grounded in systematic and rigorous research procedures.
The limited amount of theoretical information debated by the pharmaceutical sector rarely materializes in the built environment literature and thus limits its use. There

appears to be minimal or no construction research to examine the validation process and factors which influence control and hence its output of regulatory compliance. As a consequence of this the project team members suffer from limited understanding and misinterpretation of the requirements for validating a pharmaceutical facility.

1.4 Research Aims, Objectives and method

1.4.1 Aims and Objectives

The aim of the research is to construct a model of the validation of buildings that are used to manufacture pharmaceutical drug products. The model, which will be proposed in chapter four, represents a time-series dependent set of sub-processes. Each sub-process receives an input from the preceding sub-process, transforms the input and provides output to the next validation stage. Process transformations are the actual validation testing stages of the overall validation activity and occur throughout the construction process. The clients desired system output is that of regulatory compliance, the deviation between desired and actual output is affected by factors that impact on system control. These factors or problematic themes are represented by a number of research propositions which are based on understanding the differences between construction and pharmaceutical quality and control, and implementation of the validation process.

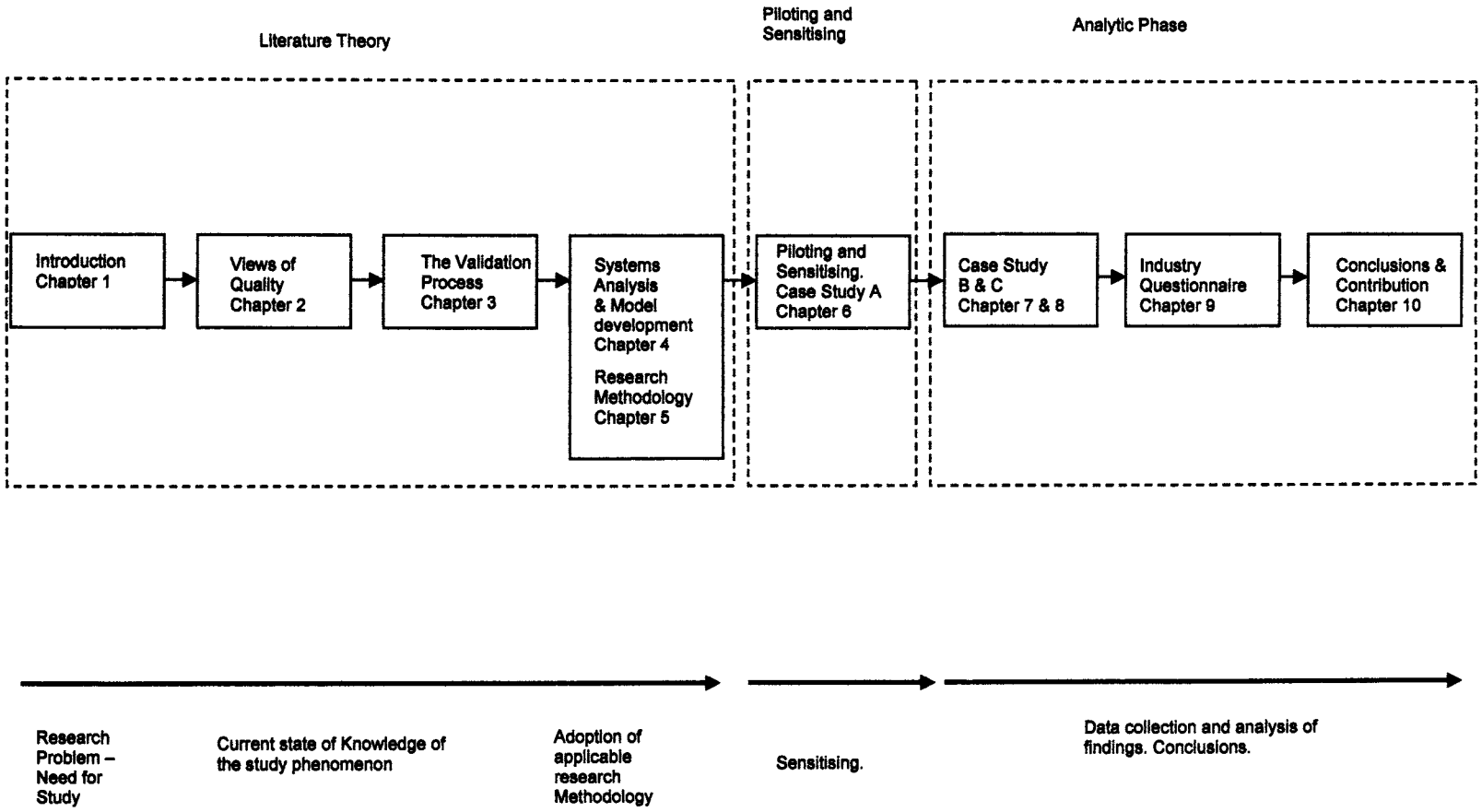
The study design consisted of three main areas which are discussed below; these are a literature survey, sensitising and pilot study and the main area of the research, case studies (analytic phase). Figure 1.1 shows the structure of research work in this study.

1.4.2 Literature Theory

The review of theory is discussed in Chapters Two and Three. Chapter Two examines the current state of theoretical knowledge of quality in both the construction and pharmaceutical sectors. The aim is to build a theoretical foundation and by reviewing the relevant literature, the relationship between the two industry sectors is examined and the different views and understanding of quality are analysed.

Chapters Three and Four are used to establish detailed study propositions and a validation process model that will be used as an analytical tool later in this thesis. Chapter Three starts with an examination of implementation of quality in construction and is followed by an assessment of implementation of quality in the pharmaceutical industry, with focus on the validation activity process stages and the regulatory requirements that govern project quality. The chapter presents an initial model of analytical classification of the parent fields in the research.

Figure 1.1 Structure of Research Work.



The chapter ends by discussing the key areas that represent problematic implementation before, during and after the construction process.

The purpose of chapter four is to evaluate the current state of knowledge of systems analysis. This analysis, commonly used to study complex problems, is then used to provide a view and understanding of the construction and pharmaceutical industries contribution to the validation process in the construction of manufacturing facilities. Modelling theory and techniques are then examined to generate study propositions and a systems model of the facility validation process.

1.4.3 Sensitising Interviews and Pilot Study

Having analysed the complex research problem by the utilization of systems theory, five key study propositions or hypothesis and a cybernetic model of the validation process were constructed. In Chapter Five the applicable research strategies that could be used to achieve objectives set out in Chapter One were examined and the research methodology of multiple case studies was identified as being an applicable method to collect primary data (Yin, 1994, p.1). The combined processes of participant observation and a grounded theory-like research approach were identified as rigorous, fair and appropriate complementary methods for social studies of this type.

In contrast with experimental and survey methodologies, the application of qualitative techniques, such as those discussed in Chapter Five and adopted as study 'tools,' are more appropriate for research questions that are based on human meaning, smaller populations and observable everyday situations.

Chapter Five established that the process of grounded theory research often commences with orienting or sensitizing concepts which generate a sense of reference and guidance about the phenomenon being studied (Bulmer, 1969) and allow for later elaboration and development of the problem examined. For this reason a pilot study and two interviews were held with two key project managers. In line with grounded theory methodology the data allowed for the successful construction of a multi-level code family tree which was then used to code and analyse two further fieldwork studies.

1.4.4 Main study

The main study collected and analysed empirical data against the model proposed in chapter four.

A research methodology model, based on a model developed by Dick (2000), is used to compare and contrast the qualitative data sets from both the case studies and from an industrial survey.

The methodology model presents four overlapping data sets which are used to generate emergent categories from the data sources of the cases and survey. The key themes of the literature review of chapters two and three, which informed the cybernetic validation model, are aligned with the field work data to establish the degree of structural correspondence.

Although the primary data collection methods were based on qualitative data sources the industry survey provided a degree of external validation and increased the converging lines of enquiry. Successful mixed mode strategies (See Pare, 2001), have used both an exploratory (theory building) and explanatory (theory testing) approach. Here a mixed-mode strategy was used in two exploratory or positivist studies. Two approaches were combined in each of the studies.

1.5 Thesis Structure

The thesis consists of ten chapters. The first chapter presents the research area, establishes the need for the present study and summarizes the outcomes of the study.

Chapters two and three identify the main area of research attention, that of the validation process used in the construction of pharmaceutical buildings.

Chapter two establishes that there are differing views and attitudes towards quality implementation between the construction and pharmaceutical sectors. From an analysis of the limited theoretical information available on the research topic, specific problematic themes that are associated with construction projects of this type are identified.

It is acknowledged that a large number of the references are used to support the propositions of this research are based on pharmaceutical industry journals and

papers, rather than articles systematically grounded in statistical research techniques. During the period of actively reviewing the available literature it became evident that the majority of the published information comes from the pharmaceutical industry, with little or no information being available from the construction sector.
For this reason it was considered of great importance to undertake an extended period of analytical research over several years to act as a participant observer in the construction and validation of a number pharmaceutical facility buildings.

Having determined the key problematic features of the validation process and established the need to provide new information and understanding on an under researched area, an analysis tool that would assist in generating the research model was discussed.

The cybernetic validation model constructed in Chapter Four was based on the systems analysis approach to solving complex problems.
Chapter Five considered various research strategies and discussed the methods, with justification, that are chosen for this study. The chapter also presents a grounded theory-like research model of data collection and analysis.

Having established study propositions and the cybernetic validation model, the next stage of the research was that of empirical data collection and analysis.

Chapters Six, Seven and Eight present the results and analysis of the primary data sources, three case studies. The first of the case studies was primarily used as a sensitising pilot study to provide an initial micro level inspection of the social setting allowing for later elaboration and development of the problem examined in the subsequent studies.

Chapter Nine presents the results and analysis of an industry questionnaire.
The survey considers the external validity of the study and the actual domain into which the case study findings may be generalized. The data is analyzed using descriptive statistics and correlation coefficients to establish relationships and differences between the two respondent groups with respect to the study model and propositions.

The final chapter, (Chapter Ten) discusses the study propositions and the initial cybernetic model is appraised. The research model is revised and study limitations are discussed together with recommendations for future work and conclusions.

1.6 Summary and Contribution

Summary

Literature on facility validation is almost exclusively produced by the healthcare technology industry and views expressed indicate facility validation is both costly and time-consuming. In addition it is stated the validation process is not widely understood outside the environment of pharmaceutical manufacture and is viewed with some negativity.

The main aim of the study was to examine why the validation activity often fails to meet its objectives by constructing a model of the validation of pharmaceutical facilities. The model was assessed through comparison of fieldwork and survey data and was revised.

The models original propositions were that the system output, that of a compliant facility, was influenced by two main observable themes; understanding of implicit regulations and implementation through system control.
Firstly, considering implementation through control, cybernetic control is achieved through goal-seeking processes to achieve compliance. The following summarizes how compliance is affected by deficient control:

a. The system transformation process was validated as a 'black box' system. This was demonstrated by multiple functional tests in the validation protocols and limited structural testing.

b. System goal states were undefined and contained embedded none compliance. This was exhibited by vague acceptance criteria in testing protocols.

c. The process output deviation from the goal was so large between events that 'swing' or 'lag' was observed. Lag is a swing away from the goal prior to feedback correction that requires a more forceful reaction to attain control. The effectiveness of control is at a maximum when the time lag between the corrective action and the process output is at a minimum. The client's complex organizational hierarchies meant that information flow was restricted and communications were slow from one function to the next.

d. Too few inputs permitted sub-process systems to become 'closed' resulting in system decay or deterioration. New inputs such as energy and information are required for the closed system continuity.

e. The limited degree to which adaptation took place in the project environment is related to the ability to respond to environmental stimuli. Some contracting organizations do not have adequate structures to recognise this stimuli.

f. Feedback systems contained limited sensory apparatus to distinguish deviations between process outputs and goal-states. This was highlighted, in case C, where the design review sub-process was not implemented by the project group and critical GMP items were omitted.
A degree of positive feedback was demonstrated by the selection of an inappropriate system which did not receive adequate quality review early in the program. This scenario displayed an element of positive feedback control whereby system deviation from its goal state increased until a critical point was reached.

The second of the two main observable themes, understanding of implicit regulations was demonstrated in the research which showed that the approach to the application of quality techniques in both the construction and pharmaceutical manufacturing industries were found to be very different. Client requirements were often not clearly understood or communicated because of limited early involvement between both groups.
Traditionally manufacturing based quality is concerned with the final product whereas construction quality is viewed in light of levels of workmanship. Both deviate from the concept of total quality and that of pharmaceutical quality.

The pharmaceutical industry is generally viewed as technological, inflexible, highly regulated and committed to research and development. The construction industry is perceived as highly contractual, with low implementation of technology and research and development.

Construction survey respondents also viewed pharmaceutical facilities as complex and survey findings demonstrated that there were differences in understanding of regulatory compliance and quality.

1.6.1 Theoretical Contribution

The theoretical contribution of the study is that it provides new information and understanding of the validation process of pharmaceutical facilities, in an area of enquiry that is under researched by the construction sector. In particular, there has been practically no empirical research of this type. A synthesis is made from data from two different industries. The study is also cross–disciplinary, where most of the case study data is gathered by participant observation in the pharmaceutical facility project environment.

The work utilizes a methodological approach that is uncommon outside the field of the social sciences. The original approach of the extended period of unknown observer participant observation has provided a holistic view of a number of construction projects. The utilization of the Computer Assisted Qualitative Data Analysis Software (CAQDAS), The Ethnograph computer program was used successfully to code and generate qualitative data that was used to analyse the case studies.

Successful application of qualitative rather than quantitative experimental techniques should be of interest to other researchers who may have only considered statistical rather than analytical generalizations as a mode of theory development.

1.6.2 Practical Contribution

The practical contribution is:

1. The research best practice model will help those industry practitioners involved in health care projects to understand the regulatory expectations and the concept of validating buildings and systems.

2. An awareness and understanding of the problematic themes that influence outcome will help better prepare the construction project manager for a project of this type.

3. An appreciation of the time series nature of the process will allow the project manager to better plan and implement the validation works together with an understanding of 'what' to validate and 'how' will help avoid the spiraling of project costs that can occur.

This chapter has provided an introduction to the research problem and highlighted the knowledge gap that exists. The aims and objectives have been established together with the applicable methodology for achieving these ends. The chapter concludes with a summary of the theoretical and practical contribution that the research has made in the subject area. A road map of the research process has provided a clear picture of the structure of the thesis.
The next chapter, Chapter Two, reviews the parent fields of this research problem by examining the body of knowledge and establishing, through the use of an analytical classification model, where the research sits in relation to the literature.

Chapter Two: Quality in the Construction and Pharmaceutical Industry Sectors

This chapter examines approaches to quality in both the construction and pharmaceutical sectors. The aim of the chapter is to build a theoretical foundation upon which the empirical study is based. By reviewing the relevant literature the relationship between the two industry sectors is examined and the different views and understanding of quality are analysed.

Chapters three and four will continue the review of the body of literature and are used to establish detailed study propositions and a validation process model that will be used as an analytical tool later in this thesis.

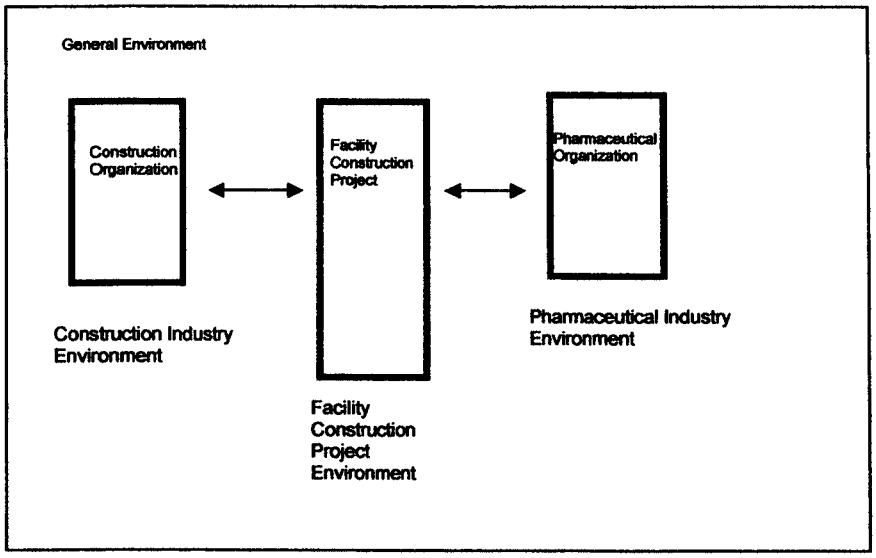
The chapter starts with an examination of the meaning of quality and the work of the quality 'gurus'. Implementation of quality in construction is scrutinized followed by an assessment of current initiatives. The implementation of quality in the pharmaceutical industry is then discussed, with focus on the validation activity process stages and the regulatory requirements that govern project quality. This chapter presents an initial model of analytical classification of the parent field of the research.

2.1 Analytical Classification

The analytical classification model, shown in figure 2.1, presents the parent fields of knowledge to which the research problem belongs. The model is used to show groupings that impact on the research and serves as a visual map for the literature review.

The review of the current body of knowledge begins in this chapter with an examination of the two predominant groupings that affect the validation industry. Chapter two and three focus on the main area of research interest, the validation of the facility construction project and chapter four develops a theoretical model based on the groupings in the general environment.

Figure 2.1: Analytical Classification



2.2 Quality: Philosophy and Models

The previous chapter established that understanding the term 'quality' is at the heart of any approach to project implementation. Quality is notoriously difficult to define and its definition can be shaped by its use. An object or item can be observed, but the attributes of quality cannot easily be classified. If an observation was made by several different people it would probably result in several very different lists of quality attributes.

There are a large number of definitions of the word quality. Some of the most universally acknowledged variations are;

> An inherent or distinguishing characteristic; a property. Dictionary (2005)

> Conformance to requirements, Crosby (1979, p.17)

> Fitness for use - Juran (1992, p.9)

and

> the totality of features and characteristics of a product or service that bear on its ability to satisfy stated and implied needs, (British Standard 5750-8, 1991, p.3)

These definitions provide a starting point for the study of quality. It is acknowledged that the meaning of the word quality can vary. Godfrey (2001) notes that:

> Unfortunately, defining quality abstractly is extremely difficult and not very useful. It's like defining the universe: Describing a portion of it seems to make sense, but extending this definition to cover all planets, stars and galaxies ultimately proves impossible.

He goes on to acknowledge that:

> Fortunately, defining quality in this way isn't the problem most of us face. We're usually trying to define it for a specific product or service, or for a key process that produces the product, provides the service or supports the organization creating them.

The acknowledgement of the necessity to define quality for a specific service or product is central to the argument that the supplier of a service must be focused on the product-service chain of that particular industry which is served. The general problem with the early quality mandates is that, in the case of 'conformance to requirements' it can be argued that if the requirements are not adequately defined and communicated then the level of conformance provided may not be sufficient.

Juran's (1992) philosophy is summarized in the 'Juran trilogy': quality planning, quality control and quality improvement. His 'fitness for use' concept makes the assumption that the use of the product is well understood. Should the user not fully understand the 'use' terminology fully then quality failure may occur. Furthermore, the use of the 'implied needs' terminology in BS 5750 also acknowledges this uncertainty of usage.

Implementation of a successful quality process or system model will therefore be dependent on the understanding the specific needs of the customer or client. The specific needs or requirements, however, vary from one industry group client to another and are not always obvious or understandable.

Thus, quality implementation models need to reflect the characteristics, process and regulatory environment of the client. Writers such as Kubal (2002) have highlighted the reasons why quality systems fail and suggest that quality initiatives are carried

out in isolation and do not include all groups and functions that are critical to quality. Some of the main reasons for failure are:

1. Lack of cooperation between various construction professionals.
2. Little technological growth in the industry.
3. Lack of focus on critical business processes and no resource support for long term improvement efforts, and lack of synergy between quality programmes and overall strategy.
4. Poor timing and pacing of TQM initiatives, that are generally crisis led.
5. Lack of measurement in all key areas, but particularly at strategic level.
6. TQM concepts and terminology are barriers to success, because there is no consensus on their meaning.
7. No supporting infrastructure for cultural change and people issues.
8. Managerial or organisational 'mind sets' that are inconsistent with TQM philosophy.

Theories of quality management by W. Edwards Deming, another of the recognized quality gurus, relate to variations in the manufacturing process and statistical process control. Deming (1986) conceived a fourteen point system for corporate improvement. The main aim of his philosophy was to fuse the whole organization together as a single entity with the goal of achieving process improvement to achieve customer satisfaction.
Unlike, Crosby's program 'the four absolutes of quality' (Crosby, 1979) which includes the statements that:

1. Quality is defined as conformance to requirements.
2. Quality improvement is based on prevention rather than detection.
3. Quality performance standard is 'zero defects'.
4. Measurement of quality is the price of non-conformance.

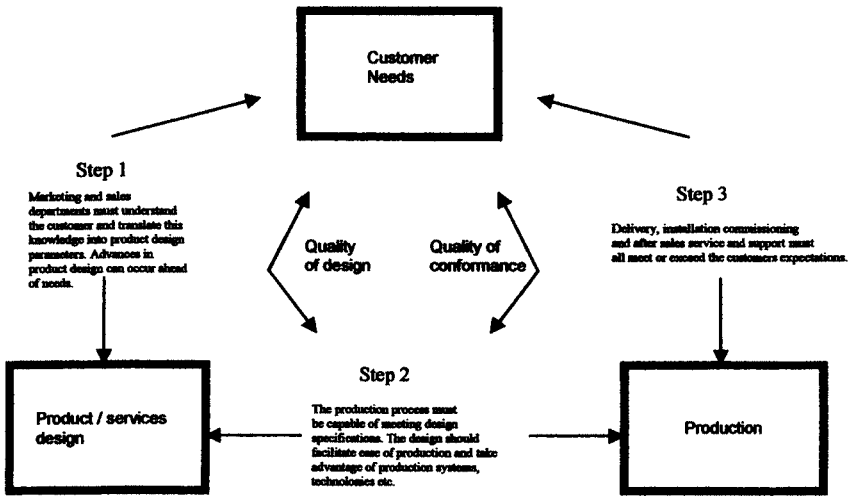
Deming believes that 'zero defects' would require zero variation in the process, which he considers impossible.
Not all quality theorists agree with each others work and teachings. It is recognized that there are conflicts in application. The main difficulty and challenge to the

practitioner is the direct application of quality to their specific industry sector or system.

2.3 Manufacturing Quality Characteristics

The simplest quality system model is based on the inspection of finished goods prior to despatch from the point of manufacture. The objective is to prevent the client receiving defective product. Samson (1991, p.137) distinguishes between the quality of the finished item (product quality) and quality of manufacturing (process quality). In most manufacturing organizations the customer or consumer of the product does not see the production process, only the product. The manufacturing process is invisible to the end user. As Samson (1991, p.137) points out 'one is tempted at first to think that what is important is product quality, not process quality'. He goes on to state that 'the way to achieve product quality is via focusing on process quality'. To apply quality to both the process and the product the manufacturing industry is managed in a total quality style. Quality is 'built in' at product design, definition, purchasing, production, marketing, logistics and delivery together with after sales and training. Figure 2.2 shows a manufacturing quality cycle model.

Figure 2.2: Manufacturing Quality Model (Samson 1991)



The main stages of the manufacturing model are;

1) The definition of customer needs by providing an interface with the consumer to continuously improve the product and focus on product specifications and characteristics together with customer behavior, delivery, flexibility and price.

2) Design of product in-line with customer needs. Questions to determine the types and needs of the customer are asked, along with defining how to achieve this level of satisfaction. This design phase will require input from all organization functions such as, engineering, marketing, finance and manufacturing.

3) Production - At this stage there is interfacing with many other areas such as facility location, location of human resources and technology.

Samson (1991, p.142) summarizes manufacturing quality as:

> a cultural/philosophical concept as well as a set of tools and techniques...in most of the worlds best companies it pervades attitudes and behaviors, being concerned with all processes and systems and ultimately manifesting itself as a high-integrity state of mind in all employees

2.4 Quality: Design and Conformance

Within manufacturing there is great emphasis on the quality of design and conformance. If quality is not considered at the product design stage, the ability to deliver an acceptable level of quality will be affected. The degree by which the finished product conforms to the design is also dependant on the manufacturing process. The different process stage inputs need to be measured and be visibly compliant with the initial specifications of manufacture. It is acknowledged that variances occur and whilst single inputs may conform, a combination of several inputs may result in unacceptable levels of variance or non-compliance. Ishikawa (1985) explains that;

> if defective products are produced at different stages of the manufacturing process, even strict inspection cannot eliminate them. If instead of relying on inspection, we produce no defective products from the very beginning - in other words, if we control the factors in a particular process which cause defective products - we can spare a lot of money that is expended for inspections.

To this end the manufacturing industry applies quality monitoring techniques at stages of the manufacturing process. Quality Control is the term used to define the operational techniques and activities that are used to fulfill the requirements of quality. Quality assurance is defined as the planned and systematic actions necessary to provide adequate confidence that the product or service will satisfy the given requirements for quality.

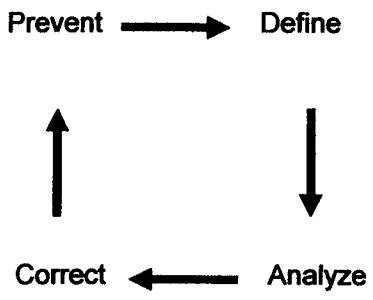
The way in which the control and assurance aspects of quality are implemented is through Quality Management. Quality Management sets the organizations quality policy and implements the overall intentions and scope. This is normally put into practice by high level management. Total Quality Management (TQM) extends the quality management to cover all the managerial control functions within an organization.

Samson (1991, p.145), states that many managers are unclear of the meanings of the terms used in TQM and often use the wrong terminology to describe the quality activity.

2.5 Quality Tools

A number of *quality improvement* tools and techniques have been commonly used in the manufacturing industry. Figure 2.3 shows a quality improvement cycle of the type used in manufacturing organizations (Marsh, 1993, p.11).

Figure 2.3: Quality Improvement Cycle (Marsh, 1993)



The improvement cycle consists of four main phases – define, analyze, correct and prevent. Each phase can be sub-divided into sub-phases which are linked to techniques or tools. The most popular techniques are discussed below.
Ishikawa (1985), employed *cause and effect* diagrams to use error data or problems with quality to determine the cause of the problems. Fishbone diagrams are drawn, which define the *effect* of the quality problem and the composition of the causal factors. The main advantages of this type of flexible mapping procedure are that the charts generate an understanding of the causal factors and the root problem, whilst providing a suitable forum for discussion.
The *Pareto principle* is used in quality control and states that a small number of problems or factors are likely to be responsible for the majority of quality problems and costs. These problems or *vital few* equate to around 20% of total quality problems which relates to 80% of costs. The principle seeks to identify the vital few and grade problem solving efforts so as to achieve the maximum gain in performance by improving the few key *high-impact* items. The Pareto principle has been used to order precedence on high-impact items in areas such as the vital few end users, products, process stages and quality stages. Other quality tools such as check sheets, histograms, scatter diagrams, graphs/stratification and control charts contribute to what is known as *Ishikawa's seven tools of statistical review*.

Another technique is *Statistical Process Control* (SPC) which views processes as having either systematic or random causes for variance. The technique stems from wartime needs for regulation and monitoring of mass produced products. Tuckman (1995, p.66) argue that *hard* techniques such as SPC are becoming less popular in favour of *culture change* as a method of quality improvement.

The *Taguchi Method* or as it is termed by Phadke, (2005) as the *Robust Design Method,* is used to increase productivity. Taguchi *et al* (2004) focuses on *noise factors* which are classed as environmental variation during product use, variation of manufacture, deterioration of the component and cost of failure in use. The analysis of optimized quality is considered at the product and process design phases. The method concentrates on improving the fundamental function of the product or process. The linkage between engineering design and the process allows for flexibility of design, making this one of the most powerful improvement methods.

The concept of robust design is explained by considering a system that receives variable inputs. The system inputs and system environment will experience variance whilst the process or transformation remains steady to ensure consistent output.

Process Capability methods measure the variance between the process and the customer requirements. Should a process produce an unacceptable level of variation then the aim of the process will be to seek *control* by;

1. Measuring the variance between process and output requirements.
2. Attempt to identify the causes of the process variations (by Pareto etc).
3. Remove the process variations, if it is economically feasible to do so.

Deming's (1982), *Plan-Do-Check-Act (PDCA)* cycle (or hypothesis cycle) is not a tool as such, it is a method that encompasses many of the previously described tools. The *plan* stage answers questions of *what*, *how* and *who* in response to the quality problem. This stage could involve the use of tools such as cause and effect diagrams. The *do* stage involves SPC techniques followed by the *check* and *action* stages which verify the cause of the problem and generate actions required to change the system.

Under and overreaction in the *action* stage is a potential problem if actions are not lead by thorough analysis. Under-reaction occurs if a change or variance is not acted upon and overreaction is a move to treat the variation which in reality is random. The action stage also includes the communication and documentation of the corrective procedures.

2.6 Pharmaceutical Quality

The literature of facility validation is almost exclusively produced by the healthcare technology industry which includes pharmaceutical, biological and medical device manufacturing sectors. The majority of literature from these sectors relates to the validation of manufacturing equipment and systems (See Berry & Nash, 1993), laboratory equipment, cleaning procedures, and computer and automated systems (See Wingate, 1997). The philosophy of the procedures employed in the validation of process systems are essentially the same as those guiding facility validation and the findings of this study may be transferable to other systems and equipment employed in manufacturing.

Various authors have recognized the effects of current regulations. De Valle (1995, p.14) suggests that factors such as plant geographical location and product market location have to be well understood to effectively manage the design, construction and validation of a pharmaceutical facility. Allan (2004, p.62) also found that the regulations have made validation costly and time-consuming. To understand why these effects occur in the United Kingdom (UK), Europe and the United States of America (USA) current pharmaceutical regulations have been analyzed.

2.7 UK (European) and USA Regulations

The Medicines and Healthcare products Regulatory Agency (MHRA) is the UK regulatory agency responsible for ensuring that healthcare products and medical equipment meet the required standards. The Agency is an executive arm of the Department of Health. In April 2003 the MHRA replaced the Medicines Control Agency (MCA) and the Medical Devices Agency (MDA).
The main activities of the Agency are to enforce the requirements ensuring compliance to standards of pharmaceutical manufacture.

In 1991 there was a harmonization of manufacturing authorizations and Good Manufacturing Practice (GMP) within the European Community (EC) and pharmaceutical inspections are now regulated by European Commission Directives. There are two main European Commission Directives that give the principles and guidelines of Good Manufacturing Practice (GMP). European commission (1991a), Directive 91/356/EEC provides information for medical product for human use and European commission (1991b), Directive 91/412/EEC gives information for veterinary medicinal products.

Article 8 of the Rules and Guidance for Pharmaceutical Manufacturers and Distributors (MCA, 2002) states that 'Premises and manufacturing equipment shall be located, designed, constructed and maintained to suit the intended operations'. It goes on to say 'Layout, design and operation must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid contamination, cross contamination and, in general any adverse effect on the quality of the product' and

'Premises and equipment intended to be used for manufacturing operations which are critical for the quality of the products shall be subjected to appropriate qualification'.

Qualification, or as it is also widely termed *validation* is 'the action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results' (MCA, 2002). The directives define those areas of specific importance as;

1. Avoidance of material or product contamination.
2. Premises maintenance operations that do not present a hazard to the product quality.
3. Appropriate lighting, temperature, humidity and ventilation.
4. Premises design to afford maximum protection against insects or other animals.
5. Prevention of entry of unauthorized people.

The focus of this research is primarily concerned with items 1, 2 and 3 of the directives as these are the areas over which the construction industry has most influence and control over.

In the USA the Food and Drugs Administration (FDA) is responsible for regulating the pharmaceutical industry. New drug products and complex medical devices must be proven safe and effective before they are able to be marketed. The FDA inspects more than 16,000 domestic and foreign facilities every year (FDA, 2004) to enforce GMP. It is recognized that the USA federal regulations are generally equivalent to those standards enforced in Europe.

2.8 Mutual Recognition of Standards

Mutual Recognition Agreements (MRA's) between EC and other countries outside of the Community are negotiated to ensure a mutual recognition of standards of GMP and compliance by Pharmaceutical companies.

Agreements of this type are currently operating with New Zealand and Australia and are expected to be adopted in Canada and Switzerland. In the USA the MRA's are in a transitional evaluation phase whilst Japan is also in negotiations with the EC.

The mutual recognition of standards will mean that the each individual regulatory agency will accept the findings of each others facility inspections and report under a MRA. Subsequently the regulatory authorities will accept each other's inspection report and as a result routine inspection by one agency in another's geographic territory will not be required.

The level of guidance given by the different regulatory authorities is general in nature and the responsibility to provide documented evidence of compliance with GMP is that of the pharmaceutical manufacturer. *Quality* therefore must be designed into the facilities and associated systems used to produce the finished pharmaceutical drug product (Odum, 1997, p.8). The success of building in quality into a facility and hence the final drug product is dependant on the understanding of GMP's and the validation program.

2.9 Summary of GMP Requirements

The study thus far has identified the main regulatory agencies, their expectations and influence on the construction of pharmaceutical facilities. Building on the definitions of the validation activity the goal is therefore to provide documented proof that;

1. The premises, the facilities, the equipment and the processes have been *designed* in accordance with the requirements of current Good Manufacturing Practice (GMP). This constitutes Design Qualification (DQ).

2. The facilities and equipment have been constructed and *installed* in compliance with their design specifications. This constitutes Installation Qualification (IQ).

3. The facility and the equipment *operate* in accordance with their design specifications. This constitutes the Operational Qualification (OQ).

4. The facility and equipment operate within their design specification to repeatedly and reliably *produce* a finished product of the required quality. This constitutes Process Qualification (PQ).

2.10 Construction Quality

Quality in the construction industry has been based on theory and techniques first used in the manufacturing industry. Construction related quality is defined by Hellard (1993, p.6) as a process where;

> the needs must be defined by the client. The inclusion of services is pertinent to construction, where both designers and contractors supply services as well as the product (i.e. the completed work). The quality of these services is vital, not only in meeting the client's requirements, but also in completing to time and budget.

Kubal (1994, p.1) defines construction quality as;

> Conformance to project plans and specifications, which will result in improved final product quality – specifically, the finished building project.

Kubal (1994, p.XV) argues that quality programs in the construction industry often fail as they are all too often never implemented beyond a review of the theory of quality experts, such as Deming, Crosby and Taguchi.
Limited implementation coupled with the highly contractual nature of the construction industry presents roadblocks to project partnering and success. Kubal (1994, p.10) argues that all parties involved in the building project establish adversarial relationships because each group considers its own legal interests as a priority above quality.

Historically the way in which a client procured a building was simple, based on a buyer-seller relationship. The process of construction has now become very complicated when dealing with large complex projects, such as those found in pharmaceutical manufacturing. An example of this complexity was the Channel Tunnel project, as described by Hellard, (1993, p.29). The project involved ten

contracting organizations and several financial institutions which formed two linked companies. Numerous arrangements were entered into with dozens of firms involved. Quality assurance techniques were used on the project, but claims spiralled and TQM seemed non-existent.

The main reasons for these quality failures were linked to:

1. The contractor and client not seeing themselves working together towards a common goal.
2. The complex pattern of relationships that existed due to the large project size.
3. Inability of all groups to meet the client's requirements.

The contribution of work from Kubal (1994) and Hellard (1993) has resulted in the identification of common factors that have influence over the quality outcomes of the construction project, these are:

1. Lack of cooperation between various construction groups.
2. Limited technological growth in the construction industry.
3. Continued reliance on outmoded QA/QC field programs for product quality controls.
4. Owner's concentration on initial building costs versus life-cycle or operating costs.
5. Transference of professional liability and risks to other project team members.
6. Effect of the technical capabilities of the field work force.

Hicks (1993, p.8) notes that quality programs are put into practice because of increased competition from other competing companies. He argues that if companies fail to produce quality products and services, they will be at a disadvantage to their competitors. Additionally, he points out that being customer focused and obtaining customer quality demand information can significantly increase product quality and perceptions of product quality. Love & Li (2000, p.139) in their paper on overcoming the problems of quality certification in the construction industry suggest that companies may see quality system implementation as 'a necessary non-productive evil that may represent extra work'.

2.11 Implications of Quality Implementation

Quality system programs have been historically geared towards the manufacturing and service industries. The process has been controlled by one organization, which has, according to Kubal (1994, p.43) internal and external customers within the company. Internal customers are those customers whose material and labour are used in the manufactured product, but who are not end users.

The construction company also has both internal and external customers but, unlike manufacturing companies, does not have a single group responsible for quality (Kubal, 1994, p.43). Kubal (1994, P.43) argues that both the client (manufacturer) and architect are both external customers and that the main contracting organization only has a contractual relationship with the client. A contractual link will almost certainly exist between the main contractor and sub-contract organizations or internal customers. The sub-contractors will provide labour, materials and equipment from other organizations and suppliers who become far removed from the quality focus of the project. Their involvement or ability to communicate and contribute to overall project quality may be non-existent or minimal.

Howell & Ballard (1995, p.334) identified the key features of uncertainty in construction and manufacturing. This work presents construction as the preparation of a prototype product. Figure 2.4 shows the key differences of uncertainty in both manufacturing and construction.

Figure 2.4: Manufacturing and Construction Project Uncertainties (Howell & Ballard, 1995)

	Start of Manufacturing Production	**Start of Construction in the Field**
What	Highly defined.	Evolving as means refines ends.
How	Highly defined. Operations plan is in great detail based on many trials. Primary sequence of major tasks is inflexible, interdependencies are documented and analysed. Positions in process determine required skills.	Partly defined but details unexamined. Extensive planning remains as situation evolves. Primary sequence only partly determined by hard logic but may change. Interdependencies due to conflicting measurements, shared resources, and intermediate products only partly understood. General craft skills to be applied in a variety of positions.
Assembly Objectives	Produce one of a finite set of objects where the details of what and how are known at the beginning of assembly.	Make the only one. The details of what and how are not completely known at the beginning of assembly.
Improvement Strategy	Rapid learning during the first units preparing for production runs.	Rapid learning during both planned and sub-assembly cycles.

Research carried out into lack of quality in the construction industry by Cnudde (1981) suggests that quality implementation fails because of the unsuitability of quality training and consequently the effect of this on the study, design and specification. The degree to which quality improvement programs have been implemented is cited as another possible cause of lack of quality.

Cnudde (1881, p.511) goes on to say that the client has considerable responsibility in the field of quality and will make the process coherent and homogeneous if he: clearly defines, selects partners properly, determines the most appropriate organizational system and is sure of the competence of the quality of performance of all the partners. Unfortunately, as previously noted, contractual formats often prevent adequate quality communication between the potentially numerous sub-contract organizations involved in the project.

Hall & Tomkins (2001, p.734) have carried out research into the cost of quality failures in the construction industry and report that communications, design mistakes, lack of planning, errors and organization are key causes why quality objectives are not met. Landin (2000, p.509) suggests that the construction industry needs to blend quality concepts from both service and manufacturing industries' as a

way of achieving quality objectives and satisfying clients requirements. It is also generally acknowledged by commentators such as Aoieong *et al* (2002, p.179) that quality and TQM practices in the manufacturing industry have been successful and, as a result, there is a growing interest to adopt these procedures to improve the overall quality of construction projects. Arditi & Lee (2004, p.125) suggest that the way to measure the quality of a construction project is by measuring conformance to a quality plan that is designed to satisfy the customer.

2.12 Attitudes and Culture

Kerzner (1995, p.1040) argues that quality as a whole is viewed as the responsibility of the client and identifies past and present views on quality systems, which are set out in figure 2.5.

Figure 2.5: Changing views of quality (Kerzner, 1995)

Past	Present
Quality is the responsibility of blue collar workers and direct labour employee's working on the floor.	Quality is everyone's responsibility white-collar workers, the indirect labour force, and the overhead staff.
Quality problems lead to blame; fault justification and excuses.	Quality problems lead to co-operative solutions.
Corrections to quality problems should be accomplished with minimum documentation.	Documentation is essential for ''lessons learned'' so mistakes are not repeated.
Increased quality will increase project cost.	Improved quality saves money and increases business.
Quality is internally focused.	Quality is customer focused.
Quality occurs during project execution.	Quality occurs at project initiation and must be planned for within the project.

These views may be significant to the way in which both industries approach and implement the validation process and will be examined in later chapters of empirical study.

The differing attitudes between the pharmaceutical and construction sector may be related to the characteristics and historical development of both industries.
In a comparison study, by Hirsch (1975, p.270), between the pharmaceutical industry and the phonograph record industry, it was found that pharmaceutical production is mechanistic and demand patterns and sales are more stable than those of the recording manufactures. The same can be said of the construction industry where each project may be essentially different and may not necessarily be followed by another project containing the same sequenced tasks.
Another significant difference noted in Chapter One is that large pharmaceutical organizations invest vast sums of money in research and development where the construction industry spends less. Ultimately the constraints imposed on an industry environment shape its effectiveness and operation. In Hirsch's research it was found that the pharmaceutical industry was more successful than the phonographic industry in performance. The reasons for this were noted by Hirsch as industry prestige, societal importance and the relationship between industry size and profitability.
However events at the institutional level have perhaps influenced the pharmaceutical sector more than the construction sector. In the pharmaceutical sector there has been a large increase in research and development and a steep increase in system testing to conform to FDA regulatory standards.
This proliferation of regulations and extent of system testing has generated a somewhat negative view of the validation industry by those external to its environment.
One of the reasons for this negativity of attitude is that validation is not widely understood outside the environment of pharmaceutical manufacture. The terminology generated around the process may confuse those from other sectors.

The following quotation from Sharpe, (1993) illustrates such a view;

> Validation has, in some circles, assumed the status of a religion with its own initiates, commandments and arcane language.

The negative view of validation is also recognized by James (1998, p.72):

> To many, the word validation has a negative connotation. Validation is still understood by many (openly or privately) as unrestrained bureaucracy,

> paperwork and procedures whose roots and logic are obscure and which serve only to down progress.

James argues that the reason why validation is viewed this way is due to the distance maintained between the Quality Assurance (QA) and engineering departments within a pharmaceutical organization. The validation process is instigated by the QA department and this distance form designing and constructing a facility is often maintained. This approach to projects has caused problems when the QA validation team or their validation service provider commences validation. James notes that this makes the final phase of construction to progress much slower and the facility is less satisfactory as its completion is delayed and compliance compromised. James (1998, p.72) also notes an;

> inherent culture clash and a lack of common language between engineers, scientists and quality assurance..the approach and outlook of many people involved in the validation process has been theoretical and often rather impractical. This has conveyed the impression to engineers that they are imprecise, impractical and unhelpful. In a typical pharmaceutical fast track project, this impression reinforces the views of in the minds of project managers, governed by budgets and time-lines, that their input is unhelpful and is seldom sought until it becomes too late to avoid.

Within the pharmaceutical industry there still exists a view that the requirements of GMP are costly, Selby (1999, p.46), time consuming and that following the implementation of the facility validation there is still project uncertainty.

Winn and Malone (1994, p.18) have argued that the traditional method of new pharmaceutical facility procurement has tended to be a painful process for the pharmaceutical client, where the client feels that the process is mysterious, complicated and uncontrollable. This *black box* view of the construction process by the client will act as a barrier to an integrated project approach. The reason for this view could be due to the complexity of the construction industry and it fragmented and decentralized nature. The large number of disciplines, suppliers and sub-contractors involved will complicate and stress the communications between the client and the different levels of project team. The *black box* view also applies to some areas of the construction industry who view the validation of the facility as a *necessary evil* that brings with it a lot of uncertainty and risk.

2.13 Summary

Chapter Two has established that the research problem straddles the two disciplines of construction and pharmaceutical manufacture and that there are significant differences between the studies' parent groupings. This impacts on quality initiatives used in the design, construction and commissioning of pharmaceutical facility construction projects.

The validation activity is described as specialist and is viewed negatively by many; the reasons appear to relate to the *black box* view of the pharmaceutical industry and lack of understanding of the regulations governing the implementation process of facility validation.

Having established the study boundaries, the next chapter, Chapter Three will focus on the specific implementation process as a means of examining why the validation of pharmaceutical facilities does not always fully meet the requirement of regulatory compliance. Those specific factors that effect successful implementation of the validation process will be employed to develop the research model that will be presented in Chapter Four.

Chapter Three: Validation of the Construction of Pharmaceutical Facilities

This chapter presents the current knowledge surrounding the validation activity and its implementation. It commences with an examination of the development of regulation governing the construction and validation of pharmaceutical buildings. In this respect, the role of the regulatory agencies, Pharmaceutical Inspection Convention (PIC) and the International Society for Pharmaceutical Engineering are analysed in the development of regulations. The focus then moves to an examination of the validation process and the current state of knowledge of process implementation. The chapter ends by discussing the key areas that represent problematic implementation before, during and after the construction process.

3.1 Pharmaceutical Industry Regulatory Expectations in the United Kingdom (UK)

The pharmaceutical industry has a high profile in society and media coverage of events, good or bad, is commonplace. Research findings, discoveries of new medicines and lawsuits against pharmaceutical companies have all led to this raised profile.

As a result legislation to control the quality of medicine and safeguard the public has been increasing since the late 1960's.

In the USA, legislation such as the Federal Food Drug and Cosmetic Act and in the UK, the Medicines Act (1968), set the framework for controlling medicine quality by ensuring the need to obtain licenses for the products and manufacturing facilities.

According to Larkin (1989, p.1), the World Health Assembly (WHA) recommended implementation of standards of GMP in 1969, for pharmaceutical products. These standards were based on the principle that 'Haphazard operations cannot be permitted in the manufacturing of substances that may be necessary to save life or preserve health'.

In 1971 the first UK GMP guide was published by the then Department of Health and Social Services (DHSS). The guide is now known as the 'Orange Guide' (because of the colour of its cover). In the USA, GMP regulations were issued in the

Code of Federal Regulations (CFR) chapter 21, by the Food and Drugs Administration (FDA). The main historical difference between the UK and USA Good Manufacturing Practice (GMP) guides are that, up until 2005, the UK guide is advisory and the US regulations are enforceable under law.

The GMP regulations cover all aspects of pharmaceutical manufacture including the manufacturing premises and environment. These regulations have influence on those designing and constructing pharmaceutical buildings and may affect for example, the quality of materials and finishes, type of HVAC system, and the degree to which systems and equipment require validation during or post construction.

GMP concepts are now widely used by many countries and some have developed their own GMP regulations.

3.2 The Pharmaceutical Inspection Convention (PIC) and FDA

In 1995 the Pharmaceutical Inspection Cooperation Scheme (PICS) was set up as part of the Pharmaceutical Inspection Convention (PIC). The PIC was founded by the European Free Trade Association (EFTA) in 1970 and was set up to provide an arrangement between regulatory bodies aimed at improving networking and increase regulatory confidence among member countries.

The initial EFTA members included: Austria, Finland, Liechenstein, Portugal, Switzerland, Denmark, Iceland, Norway, Sweden, and the UK. In 1993 PIC membership was expanded to include Hungary, Ireland, Romania, Germany, Italy, Belgium and Australia.

The PIC is a legal agreement between countries with treaty status, whilst the PICS is a non-legal cooperative agreement between regulatory authorities. PICS promotes the exchange of information and methods for achieving what Tribe (2002, p.51) calls 'uniform and effective inspections'. The PICS committee promote areas such as validation in pharmaceutical manufacture, training of inspectors and global harmonization of GMP. One of the main aims of PICS is to minimise the duplication effort in the development of GMP guides and documents. The PICS work closely with the EU and European Medicines Evaluation Agency (EMEA) and the expert working group (Q7A) of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH/FDA GMP Guide for Active Pharmaceutical Ingredients (API) was initially

conceived from PICS convening a industry/government conference in 1996 which addressed the topic of international harmonization of GMP's on Active Pharmaceutical Ingredients (API's).

In FDA (2001), Guidance for Industry (Q7A), the FDA recommend that where buildings are used for manufacture of API's should be *located, designed and constructed* to smooth the progress of facility *cleaning, maintenance and operations* as appropriate to the *stage* and *type* of manufacturing process. Space requirements, prevention of contamination, flow of materials, defined areas of usage, lighting and containment are all areas of importance to the FDA. Not only the facility, but the utility and water systems that have an affect on product quality should be qualified, monitored and reported upon if control limits are exceed. However, the guidance on achieving provision, qualification and 'adequate ventilation, air filtration and exhaust systems' is limited.

The FDA (2001) notes documents used in manufacturing and validation should comply with written procedure and should follow the pattern of preparation, review and approval. Control of documentation that records details of issuing, revision, superseding, withdrawal and histories is also suggested. Other requirements relating to validation documentation in FDA (2001) include:

1. Documentation retention.
2. Specific details for completion of documentation such as validation protocols.
3. Availability and prompt retrieval of documentation.
4. Electronic signatures.

The FDA (2001), outline validation requirements in more detail. The FDA urges the adoption of a validation policy clearly: indicating the manufactures approach to validation. The FDA also suggests that the process of identification of critical parameters or attributes that are critical to product quality and purity, is used as a method for addressing validation activities. This appears to be the basis for the current ISPE V model of validation.

The guidance stresses the need for a documented approach to validation, acknowledging the utilization of review and approval techniques by quality personnel and other *designated units*. There is no specific definition of the *designated units* term; this is left open to interpretation. Writers such as Dominy & Fazio (1995, p.50) and Berry & Nash (1993, p.351), recommend a multi-disciplinary

approach involving those departments and organizations that are critical to the process. The FDA (2001) also proposes that reporting actions, observed deviations and the correction of deficiencies should be appropriately documented within the validation process. Additionally the use of justification with regards to documentation variations is advocated. These techniques are used to help improve the clarity of the documentation that is used to demonstrate compliance.
With respect to the timing the FDA suggest that critical systems and ancillary equipment *qualification* is undertaken prior to commencement of *process validation.*

Terminology used by the FDA, which is then adopted by industry practitioners, is sometime met with confusion. The terms validation and qualification have been used for many years and have been viewed as having the same meaning. Qualification means to make competent or fit or legally entitled and validation or valid means executed with proper formalities, legally acceptable.
The FDA Q(7)A and EU Orange Guides do not provide any specific information on the implementation of validation activities and validation master plans. The activities of Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ) and Process Qualification (PQ) are recommended with a brief description of the purpose of each. The guidance does not suggest any implementation schedule for carrying out the validation activities in relation to the construction of the facility.

In Europe the European Commission (EC) has documented GMP guidelines in European Commission (2001), (2001/83/EC), which is to be superseded in October 2005 by European Commission (2004), (2004/27/EC). This documentation affects all companies holding a manufacturing authorization. The legislation requires manufacturers of API's, which are located in the European Union (EU), to provide evidence that manufacture was in accordance with EU GMP's. This legislation now provides a legal basis for inspection.
Franklin (2005, p.29) argues that the regulatory organization responsible for inspection of manufacturing facilities has not, in the past, been clear in their intentions.
Inspection responsibility is that of the authorities in the member state where the legal requirements must be ensured. For example, if a manufacturer located in France is

using an API which comes from England, then the UK authorities are responsible for inspecting the French manufacturer for compliance.
The new 2004/27/EC directive proposes to introduce a *certificate of GMP*. GMP certificates will be entered into a community register, which will also be used to record manufacturers not complying with GMP. The advantage of a community register of compliance with GMP would prevent two or more member countries carrying out audits at the same API manufacturer. Another advantage of proposed GMP certification, relates to Mutual Recognition Agreements (MRA) and where there is a need to inspect a foreign countries, (none EC), facility then the community register holder can be checked if a new inspection is required or if a recent inspection has taken place.
The timetable for the introduction of the new directive, in 2005, is considered by some in the EC as too short, however, Franklin (2005, p.29) notes that 'officials at the Commission take the view that these proposals to introduce GMP for API's have been known since September 1997 and the GMP guidelines themselves were published by the commission in July 2001 as Annex 15 to the EU GMP Guide so in actual fact the 'transition period' is at least four years. The affect on construction and validation of pharmaceutical facilities is likely to be wide reaching and may result in an increased focus on GMP activities and compliance.

The FDA does not actually approve pharmaceutical facilities, it is the product manufactured in the facility that is the subject of approval. The filings submitted to the FDA for drug products manufactured in the facility are subject to approval. New Drug Approvals (NDA) and Supplementary New Drug Approvals (SNDA) are required prior to distribution. FDA inspections and pre-operational reviews are audits that are not all encompassing. It is the manufacturer of the product who is responsible for design, construction, validation and operation of a plant in the proper manner. According to Avallone (1984, p.17), the purpose of the review process is to only offer the best opinion whether the new or modified facility would comply with current GMP regulations.

Berry & Nash (1993, p.351), have noted that validation standards evolve through interpretation of regulatory guidelines and from industry conference papers and periodicals.

Within pharmaceutical organizations the validation program involves numerous departments who all have an input into interrelated validation programs such as change control, Standard Operating Procedure (SOP), product validation, engineering and training. The importance of the integration of interrelated departments is stressed by Berry & Nash (1993, p.351) as being a major factor in successfully implementing the validation program.

Validation program input from departments responsible for engineering, compliance, manufacturing, health and safety, technical services, compliance, training, research and development and quality assurance are seen as vital for project success. This integrated approached is taken further by Dominy& Fazio (1995, p.50), who suggest that the architect, engineer and construction manager should be included in the project team at an early stage of the project.

Signore (1993, p.14) points out that early involvement with the relevant regulatory body is desirable and suggests that pre-operational reviews are widely accepted as an effective way of bringing the local inspectorate into the project environment. He also states the advantages of using the intensive multi-team coordination approach to construction of new facilities.

3.3 The International Society for Pharmaceutical Engineering (ISPE)

As previously noted, validation legislation can be vague and interpretation can vary. This has been recognized by the International Society for Pharmaceutical Engineering (ISPE), who have published a series of guides in co-operation with the FDA. They are known as *baseline* guides and are neither standards nor regulations. The guides are intended to provide an industry baseline in the absence of consistent and widely accepted interpretation of *some* regulatory requirements. These documents have been produced in response to a *ratcheting effect* in the cost of new facilities and acknowledges the fact that the main driver of this increased cost is the uncertainty about regulatory compliance.

The ISPE baseline philosophy is discussed by Wood (2001, P.51):

> *Good Engineering Practice (GEP)* makes a significant contribution to meeting the regulatory demands of the pharmaceutical industry. Where engineering systems may have a *Direct Impact* on product quality, supplementary *Qualification Practices* (in addition to GEP and Commissioning) are required to fully address pharmaceutical demands. The baseline approach is to restrict the application of qualification practices to direct impact systems and build on the contribution of GEP and commissioning. Good Engineering practice is a satisfactory approach for *Indirect or No Impact Systems.*

The guides attempt to make the distinction between GMP technology and non-GMP technology and the difference between direct and indirect impact systems and their effect on product quality.

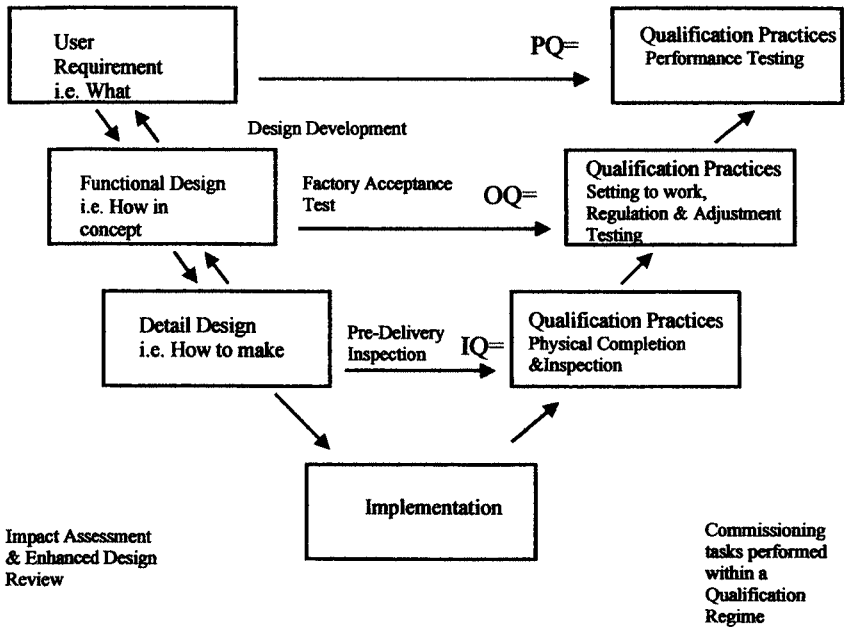
The ISPE (2001) suggest a risk based approach to validation is adopted with a system impact assessment carried out to determine what level of commissioning and qualification is required. The assessment is based on determining what impact the system has on product quality, with the distinction being made between direct and indirect impacts.

Understanding what systems and services require validation is essential in reducing the unnecessary costs associated with trying to validate every site system. The guides provide a starting point to aid understanding of regulatory requirements, but the fundamental problem is that they are almost unheard of within the construction industry.

The ISPE adopt the use of a V model, ISPE (2001) as a method of describing a relationship between User Requirements (UR) and the specifications prepared to meet the requirements. It also discusses the hierarchy of inspection and testing to be included as part of the validation.

The V model is a representation of a waterfall model which is also commonly referred to in computer software testing literature (Royce, 1970).

Figure 3.1: The ISPE V- Model (ISPE (2001))



The V-model for a direct impact system, one that has a direct impact on product quality, suggests that the qualification tasks are equivalent to the commissioning tasks and are enhanced by more detailed qualification procedures. This approach suggests that to validate a system successfully the performance, construction and operational requirements of the systems should be known. The qualification stages of PQ, OQ and IQ are used to test and verify the user requirements, functional operation, construction and installation.

The V model also considers the use of Factory Acceptance Tests (FAT) and Pre-Delivery Inspections. A criticism of these actions is, that while they provide an assurance that quality has been designed into the system and operation can be displayed, the actual validated status of a system has to be demonstrated in its final place of installation. Transportation between the supplier and the facility can result in system damage or interference. Factory calibration may also be effected in transportation and whilst FAT's increase the level of assurance and contribute to validation procedures, they are not a substitute for in-situ validation.

The ISPE philosophy stresses the need for integrated working between engineering and QA disciplines. It is proposed that the engineering departmental responsibility should be to communicate effectively the operation of engineering systems and their potential impact to the QA organization involved in the project.

3.4 The validation Process

3.4.1 Characteristics of Pharmaceutical Validation

Validation is characterised by the diverse collaboration of experts that interact in the task environment. Typically these are construction project managers, Heating, Ventilation and Air Conditioning (HVAC) engineers, calibration engineers, validation engineers, quality assurance experts, plant and maintenance engineers, ~~technologists~~, chemists and microbiologists.

Generally the validation process is subjected to precise time schedules. Historically the validation works have been at the final stage of a project prior to taking new processes and facilities into routine operation. Hence pressure is exerted on those involved in the finalization of the validation process.

Whilst, pharmaceutical buildings have been noted by Bender (1996, p.30) as costly the validation activity requires the input of highly specialized personnel and expensive technology. This differs from the provision of ordinary commercial buildings since most pharmaceutical buildings need to comply with GMP regulations prior to operation.

3.5 Planning - Pre-Qualification Activities

3.5.1 User Requirements Specification

The User Requirement Specification (URS) outlines the intent of the project and provides a formal document of the requirements of the user. Wingate (1997, p.52) argues that if the URS is not sufficiently detailed enough it may cause major problems further on in the project and that inconclusive requirements should be avoided as they hinder effective design. The URS must be prepared for all important systems. Systems in this case can mean a single room, a piece of equipment, a utility or a group of items. The information should be specific and understandable to the

user and contractor. The URS document is normally produced by the client but assistance may be requested from a contractor or vendor.

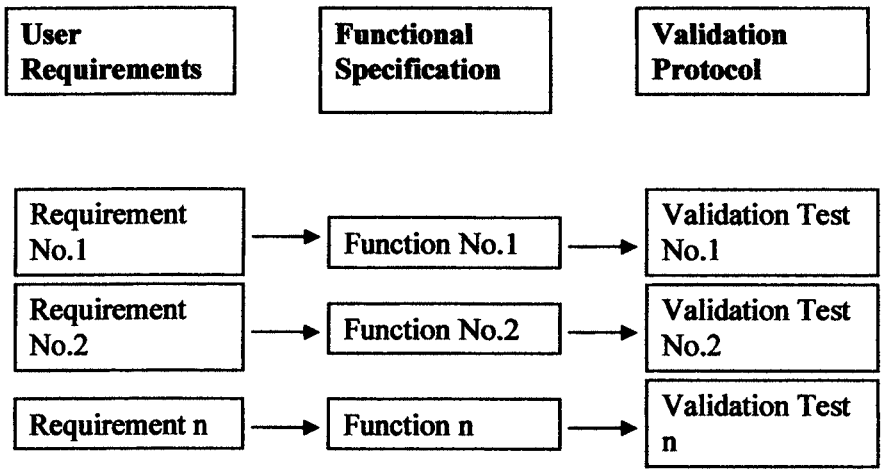
The URS is essentially used to verify the detailed design specifications produced by the project design team actually incorporate those requirements set out by the client. A multidisciplinary team approach to the production of the document is suggested by Wingate (1997, p.53), with the document being written prior to any design or installation work.

The URS outlines the critical system parameters that should be tested and should also consider how test are implemented. Vague specification can lead to inadequate acceptance criteria and if the URS is not produced by a multidisciplinary group, could have the view point of only one particular author thereby lacking completeness.

3.5.2 Functional specification

The Functional Specification (FS) is the design team's response to the URS. The FS provides a design solution for meeting the user's requirements. The importance of approving the FS by the client is stressed by Wingate (1997, p.57). The approval process ensures that the design solutions provided by the construction group will produce a facility that meets the GMP requirements of the client. Wingate (1997, p.57) states the use of documentation audit trail will help trace where requirements have been specified and tested. Figure 3.2 shows where compliance, omissions and non-conformances in relation to the URS can be identified.

Figure 3.2: Documentation Audit Trail (Wingate 1997)



3.5.3 Validation Master Plan

The validation plan, describes the project, provides details of the types and quantity of validation documentation to be generated as part of the project and gives information on resource requirements and responsibilities.

A typical plan is made up of the following sections:

- The aim of the plan.
- The project responsibilities.
- Description of facility, equipment, services etc
- Validation protocols.
- Overall strategy.
- Matrix of validation protocols.
- Program.
- Change controls – controlling of critical changes to facility, equipment or process.

The plan has four clear uses:

1. At project inception – To allow validation to be built into the project and make team members aware of the requirements.
2. Throughout the project - To allow the project manager to keep track on progress.
3. At completion - To give a measure of completeness of the validation side of the project.
4. At Audit – The plan will give auditors an understanding of the company's approach to validation and the set up and organization competence of all validation and project activities.

Lange, (1997, p.18) suggests that if input from numerous disciplines is made early enough in the project it can help to pinpoint areas of concern in the overall design, construction, modification or development program.

The Validation Master Plan (VMP) is used to address compliance questions of 'what', 'why', 'how', 'who' and 'how much'. The 'what' questions refer to identification of systems and sub-systems that may or may not require validation and justification or 'why' questions are answered to demonstrate that regulatory guidance

has been considered. The plan should also give consideration to methodological approaches and scheduling.
The plan should state ''how much' validation is required. Some systems will require static system tests such as those typically covered by the installation qualification stage of validation. Other systems that are dynamic in operation may require suitable dynamic testing which are commonly addressed by operational qualification validation.

The VMP should be prepared at an early stage in the project; Wheeler (1994, p.54) suggests that 'the master plan should be developed as soon as possible when design documents are available'. Dream & Jester (1997, p.93) recommend 'early involvement' as a way to anticipate demands on time and resources and to avoid changes at design and construction. Lien & Schultz (1991, p.17) and ISPE (1998, p.15) recommend that the VMP should be formulated during the conception phase of the project. They argue that both customer and supplier personnel should interact to form an organized team who approach the validation of the total system in a structured manner. Alperin (1984, p.19) suggests that a delay in developing the master plan can result in a delay in the commencement of facility manufacturing. The VMP may also be used as starting point for the regulatory body to conduct a joint review of the proposed project. The view of Alperin (1984, p.18), is that if the master plan is found to be acceptable by the regulator, then it represents a commitment by the organization to follow a described plan. The advantage to the organization is the perception of ready acceptance and approval by the regulator at the final inspection prior to production start up. The ISPE (1998, p.14), also note that pre-construction meetings with the regulator can be valuable.
The importance of the VMP as a *guide* to compliance is stressed by Maynard (1993, p.84);

> a well known FDA investigator stated that he views planning documentation to be one of the most reliable predictors of GMP problems and that during the initial stage of an FDA audit it is customary for him to request the validation plan documents. The reaction by management to such a request often will reflect much about the quality of the firm's documentation.

Maynard (1993, p.85), suggests that VMP's have been developed after the completion of the project as a *defensive measures*. Retrospective documentation procedures underline the organizations lack of understanding of the potentially useful purpose of such a plan. Timely generation of such a document could lead to identification of areas of concern in the overall design, construction, modification or development program.

Adamson (1992, p.16), in a paper describing an approach to validation of design, engineering, construction and pre-commissioning of new pharmaceutical facilities notes that the VMP should consider the full *life-cycle* of the project, evolving from a preliminary front-end document to a developed plan that changes with the dynamics of the project.

The plan must therefore be continually evolving and cover all prospective, concurrent and retrospective validation activities as well as periodic re-validations. There are several pre-requisites with a document such as the validation master plan. The document must be in a written format explaining the how's and why's, showing that all parties have had the opportunity to discuss all the issues. The document must be seen as being appropriate to the task. It is apparent that the success of the validation and testing of the project, indeed the overall project, will be greatly influenced by the writer of the master plan (Maynard, 1993, p.86). The plan provides a structured model that allows the project manager to measure performance of the project. This underlines the need for a collective input from all team members. Those involved should include the traditional members of the team such as engineer, architect, client, construction project manager, sub - contractors but also the clients validation engineer (in–house or external consultant), commissioning engineer, equipment vendor (supplier) and process engineer.

3.5.4 VMP Formats

There are many formats of VMP's, where the structure is dependant on the organization, project complexity and the plan's writer. There are however common themes of structure which include; project overview, system description, acceptance criteria, responsibilities, documentation and schedules.

However, Maynard (1993) proposes that format is independent of content and subscribes to the adoption of an industry standard format. Commonality of format for

large organizations is put forward as a way of assisting communications, validation intent and auditors, both internal and external.

Acceptance Criteria should be included in the VMP and be developed for each area of validation. The acceptance criteria will be based on recognised standards, that should be referenced and appropriate to the test. Clear and unambiguous criteria, that are easily understood, should leave the auditor with no room for alternative interpretations.

Maynard (1993, p.86) commentary of validation planning notes that;

> a senior investigator recently wrote that if the validation master plan does not include organized, clear, definitive acceptance criteria, then the validation of systems can be suspect of not being properly planned and executed and if the validation master plan does not define the methods of documentation verification review and approval then it is simply flawed.

3.5.5 Design review/Design Qualification

European and American Regulatory Agencies have, as Chew (2003, p.30) states, 'an expectation' for Design Qualification (DQ) for facilities that manufacture Active Pharmaceutical Ingredients (API) and bulk biotech facilities. The DQ or Design Review (DR) is an examination of the project design and GMP requirements. The objective is to meet the GMP requirements of the facility and the design is a methodological way of achieving or obtaining those regulatory requirements. Chew (2003, p.32) makes an important point in that;

> there may be many ways to achieve a requirement, hence, whether or not the design is met is secondary: if GMP requirements are met, then the facility, equipment and systems are in fact *qualified,* whether or not they met each and every design attribute contained in drawings and specifications.

Chew argues that regulatory compliance may be achieved without fulfilling the full design requirement of the system. This indicates that building systems may include additional features that may be seen as unnecessary when considering the quality functions of DQ. At the design qualification stage analysis of function and quality

attributes should be addressed by a multi-disciplinary team who are able to identify unnecessary project cost that provides no additional value to the installed system.

At design stage Leach (1990, p.33) has identified certain items that sit outside the domain of 'normal' construction projects. These issues can introduce *project uncertainties* into scheduling and timing of installation and hence validation activity. He cites several examples:

Delays in design completion
Due to the large number of user reviews, revisions of the design late in the design phase will affect the commencement of construction activities.

Delays in Equipment Delivery
The manufacture of large items of manufacturing equipment such as 'built-in' plant i.e. autoclaves, tray driers and tablet coaters, require long lead times. Delivery of such items and their integration into the facility therefore requires very careful planning and consideration at design stage to prevent any initial delay.

Existing Facility Interfaces
Where new facilities are constructed within existing plants, integration of existing utilities, services and production areas must be carefully scheduled to maintain on-going production. Leach (1990, p.11) notes that alterations to the installed equipment or building systems may also affect the validated status of the facility. A subsequent impact assessment could result in the need for re-qualification.

Project termination: Commissioning and Facility Start-Up
The project termination phase requires detailed organization between the construction project manager and the validation service provider responsible for facility validation.

Leach (1990, p.13) stresses that;

> the greatest benefit to the overall project will only be achieved if the scheduling effort is viewed as a mechanism to plan and communicate the approach to successfully accomplish the project to all participants.

Additionally Nichols and Preston (2000, p.54) argue the importance of design documentation stating that the design data includes all the detailed specification for all elements of the system to ensure compliance is 'built in' to the URS and FS.

In summary, the validation sequence of events would typically be as follows:

1. Generation of project URS.
2. Design of facility and FS. This confirms that the design meets the requirements set out in the URS.
3. Preparation of Validation Master Plan.
4. Production of a Design Qualification (DQ) protocol to record the design review.
5. Installation Qualification (IQ).
6. Operational Qualification (OQ).

In terms of timing the URS and FS are the primary project documents produced followed by the Validation Master Plan and then the DQ, IQ and OQ protocols. However, it is recognised that validation implementation may not always follow this sequential pattern of activities and the project characteristics may differ from project to project. The consequences of such actions are examined later, in the analysis of the case study data and are presented in chapters six, seven and eight.

The issues identified by Leach will be further developed in this chapter and be used in the development of a number of the research propositions to form the basis of the analytic study presented in chapter 4.

3.5.6 Installation Qualification (IQ)

Installation Qualification is associated with the construction and installation of the building and its services that are critical to the product quality. Its function is to confirm through defined procedures and documentation that the systems are installed in accordance with the design. This underlines the importance of firstly undertaking a GMP review of the design.

To confirm that the facility construction and its systems are installed in accordance to its design requires the comparison of the actual installed system with that of the designed system. Pre-defined acceptance criteria will often be developed at the

design stage of the project and are used to determine whether the installation test passes or fails.

If the final quality of an installed component or system can be affected by the particular installation technique, a measurable acceptance criteria that allows for corrective action should be established. The acceptance criteria would normally be developed and documented by the validation project team in conjunction with the project team.

Specific acceptance criteria for building materials and systems are discussed by Leach (1990) and include *physical, performance and procedural* characteristics. *Physical characteristics* may include the components dimensions and the allowable deviations from the specification in finite terms. *Performance characteristics* of a component or system will relate to a specific measure of performance applicable to the test specification. *Procedural characteristics* will document the specific testing methods and should include procedure, duration, equipment specification, calibration, witnessing, and documentation procedures.

This stage of the validation activity is often referred to as the *static testing phase.* Testing can be classified as static or dynamic. Roper, (1994, p.9), has researched the role of testing in computer software, notes that static techniques are those that examine systems and include activities of inspection, symbolic execution and verification. Dynamic testing relates to techniques of generating test data for execution by the system. Validation techniques also follow the same pattern of static and dynamic testing where the design and installation tests consist of examination, comparison and verification of the system and are static in nature. Operational qualification tests are normally dynamic and are generally utilized to check the facility across its operational range.

The European Commission (2001), Annex 15 states that:

> 11. Installation qualification (IQ) should be performed on new or modified facilities, systems or equipment.
> 12. IQ should include, but not be limited to the following:
> (a) installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;
> (b) collection and collation of supplier operating and working instructions and maintenance requirements;
> (c) calibration requirements;
> (d) verification of materials of construction.

A criticism of the regulations is that the specific details of procedures required for adequate testing of items such as materials of construction and calibration are not identified and interpretation is the responsibility of the reader. Instrumentation criticality and direct or indirect system classification is not considered. This limited level of detail is one of the main drivers that Woods (2001, p.50) suggests increases project costs.

Calibration Process

An essential part of any validation program is the calibration of systems and components. Calibration and validation are closely linked in regulatory compliance. Calibration is 'the process of measuring or comparison with a standard of the correct value of each reading on a measuring instrument where the standard is maintained by an international or national organization', Dictionary (2005). In the same way validation measures and compares compliance to a standard. The fundamental difference between calibration and validation is the definition and perception of the standard and the prescribed way of measurement. Calibration standards are generally well understood and are numerical measurements, whilst validation standards are not well understood and methodologically less specific.

In facility validation there is a critical requirement to measure variables accurately. As Dream (1994, p.78), comments 'any effort to proceed with validation without having first established the accuracy of the instruments used in the operation, monitoring and testing of the process is worthless'.

3.5.7 Operational Qualification (OQ)

Functional requirements of those building systems that are deemed to require validation are subject to operational qualification tests. The OQ protocol documents the test procedures, acceptance criteria and test results.

European Commission (2001) Annex 15 states that:

> 13. Operational Qualification should follow Installation Qualification.
> 14. OQ should include, but not be limited to the following;
> (a) tests that have been developed from knowledge of processes, systems and equipment;
> (b) tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as 'worst case' conditions.
> 15. The completion of a successful Operational Qualification should allow the final calibration, operating and cleaning procedures, operator training and preventative maintenance requirements. It should permit a formal 'release' of the facilities, systems and equipment.

The regulations governing operational test are, like the IQ test recommendations, also vague in content. Statement 14(a) indicates that tests will be developed from the writer's knowledge of the processes, systems or equipment. It is therefore essential to ensure that there is a skills and experience match between those producing the validation service and the complexity of the facility and systems.

As highlighted, the validation activity suffers from numerous problems associated with understanding, interpretation and implementation of current Good Manufacturing Practice regulations. Commentators such as the ISPE (2001), Christoffersen & Jespersen (2003), have recommended that validation of facilities should be implemented as a sequential set of time series processes (DQ, IQ, OQ). There are also other factors that may influence the outcomes of the validation of facility construction. They are discussed below;

3.6 Experience

In comparison with disciplines like engineering, chemistry or biology validation is a relatively new discipline. James (1998, p.72) argues that many of those in senior positions within validation service organizations do not fully appreciate its beneficial contribution to the project as a whole. He goes on to say that;

> Since it was never part of the world in which they gained 'hands on' experience, it is often viewed with mistrust, as a means to an end and associated with unnecessary red tape.

James argues that many contractors' knowledge is based on practical experience gained from their involvement in pharmaceutical projects, without the advantages of a detailed understanding of the validation process and regulatory compliance. Consequently, this basic level of knowledge is used as the basis for preparation of tenders and previous mistakes made are repeated on future projects.

Within the pharmaceutical industry itself there appears to be a lack of experienced validation personnel. James points out that this had led to a manpower shortage resulting in people being brought into the industry from differing backgrounds. Such lack of experience of personnel has meant that those entering the industry may not receive adequate training within the project environment. Importantly, James highlights that as pharmaceutical engineering departments are run down, in favour of outsourcing, the project engineer, who is generally the construction project interface, cannot devote enough time to his or her project tasks. Contract or co-opted personnel may assist in such situations but there is unlikely to be mechanisms within the project structure for feedback and appraisal.

Experience of the validation process is one facet that is required by validation personnel. Other areas of specific knowledge that a validation service provider should posses have been identified by Bauers and Hargroves, (1996, p.38), as:

1. Technical background in process engineering and mechanical systems engineering.
2. Understanding of the reasons for validation.
3. Current awareness of validation procedure.
4. Ability to envisage operating scenarios and methods.
5. Good communications skills.
6. Ability to meet deadlines.

Generally all of these factors above relate to the education and experience of the individual validation service provider, an area that will be further examined later in the thesis.

3.7 Planning - Timing and Cost

Data regarding cost and time planning of facility validation activities is not widely available to the construction manager. As Bender (1996, p.30) points out the construction of pharmaceutical buildings can be both costly and complex. Bender (1990, p.30) suggests that the pharmaceutical and construction industries are both competitive and secretive and have not shared cost data regarding the construction of facilities.

Historically, validation of pharmaceutical facilities failed to meet its objectives because early validation was generally retrospective. Today most companies acknowledge that validation is required although how much and the time requirements of the process are still not well understood throughout the industry, James (1998). As the process is relatively new implementers have performed and documented excessively, in an attempt to obtain regulatory compliance, regardless of cost. James (1998, p.73) points out this has perpetuated unrealistic documentation requirements and promoted fears of excessive implementation costs and time requirements.

The fieldwork section of this thesis is concerned with data gathering from oral solid dosage facility construction projects (see chapter 6, 7 and 8).

With reference to figure 3.3, Alan (2004, p.63) suggests that validation costs for a secondary oral solid dosage secondary pharmaceutical facility, as a percentage of the total installed costs, are in the region of 5 – 9%.

Figure 3.3: Typical Engineering, Construction Management and Validation Costs (Allan (2004))

	Engineering	Construction Management	Validation [1]
Bulk Chemical Active Pharmaceutical Ingredients (API)	10 – 14%	5 – 11%	5 – 7%
Bulk Biotechnology (API)	14 – 18%	5 – 11%	10 – 15%
Secondary Pharmaceuticals (Solid Dosage, Liquids and Ointments)	7 – 10%	4.5 – 8%	5 – 9%

[1] - Includes owner spent material and plant labour costs associated with validation costs.

Figure 3.3 shows the validation costs, as a percentage of total installed costs, vary with the type of facility construction. Validation costs for bulk chemical facilities are lower than the more complex secondary production facilities, which are in turn less complex in manufacturing process and building systems than that of biotechnology facilities. The figure demonstrates that the manufacturing process and the facility housing the process has a direct influence on the magnitude of the cost and amount (time) of validation required.

Items such as environment control requirements shape the form and quantity of validation testing. See figure 3.4.

Figure 3.4: Control Requirements (Schwartz, 1994)

Facility Type	Control Requirements	Control Range Tolerances	Other Considerations
Offices	Temperature Humidity	Wide Wide	Computer loads and other office equipment, outside air quantity to meet indoor air quality needs.
Laboratory	Temperature Humidity Pressurization	Narrow to tight Narrow to tight Narrow to tight	Internal heat loads, safety, exhaust requirements, biological and chemical fume hoods, air particle background.
Animal Housing	Temperature Humidity Pressurization	Narrow Wide to narrow Narrow to tight	Flexibility to house different species at different environmental conditions in the same room.
Process Operations	Temperature	Wide	Safety and exhaust requirements.
Pharmaceutical	Temperature Humidity Pressurization	Narrow Wide to tight Wide to tight	Safety and exhaust requirements, air particle background, dust collection, process requirements.
Distribution	Temperature	Wide	Safety and exhaust, stability of product.
Sterile Operations	Temperature Humidity Pressurization	Narrow to tight Narrow to tight Tight	Air particle count and background, safety considerations for both chemical and biological agents.
Containment	Temperature Humidity Pressurization	Narrow to tight Narrow Tight	Pressurization controls are critical as is possible exhaust treatment, safety issues.

Figure 3.4 indicates the operational parameters required for different healthcare facility types. The assessment of criticality will be based on the impact of the specific control requirements on the product only. The impact of control requirements of an office space on quality will be zero, as the space utilization is not directly related with the process. Pharmaceutical, sterile or containment spaces would require narrow to tight control over environmental parameters as the systems serving these spaces would normally be classed as direct impact.

Anisfeld (1998, p.56) suggests a document matrix can be used to identify which validation documents are required. This approach lists the main items of plant that are seen as critical to the space or system. The following is an example of the decision matrix that may be used for utility services required for a new clean facility;

Figure 3.5: Document Decision Matrix. (Anisfield, 1998)

Item	DQ	IQ	OQ	PQ
Purified Water	✓	✓	✓	✓
Steam	✓	✓	_	✓
Compressed air	✓	✓	_	_
Air conditioning	✓	✓	✓	_

The decision matrix is ultimately based on the validation service provider's knowledge of the process and systems. Once the types of documentation and tests have been established the next stage is to estimate the time requirements of developing the documents, obtaining agreement to the documents and finally executing the tests. Basic methods entail estimating the number of documents that are considered necessary for the project and multiplying by the number of hours that is needed to develop these documents.

The obvious disadvantages of these methods are that protocols differ and average protocol content and time required is generally difficult to estimate. The individual's knowledge of the validation process and experience of similar projects will influence the ability to accurately estimate duration. The procedure of estimating cost and time requirements appear to be under-developed and may significantly impact on project success. As such planning is considered important in the research and is considered further by analytical methods.

3.8 Complexity

Projects for the construction of pharmaceutical facilities differ from many other construction projects because of the complex manufacturing processes housed within the facility and the critical nature of products produced. Tedesco & Titus (1995, p.22) suggest costs of items such as finishes, services installations, support systems, utilities and other hardware are far more significant than for non-pharmaceutical manufacturing facilities of equivalent size.

Technical complexity is defined by Woodward (1969, p.203) as;

> the extent to which the production process is controllable and its results predictable.

Complexity can also be noted as 'the degree of organizational diversity in terms of activities and operating environment' Child (1984, p.27).

Systems that employ a high level of technical complexity are commonly integrated into the building. Systems such as Building Management Systems (BMS), that are used to control and monitor highly serviced *clean* manufacturing areas, are often integrated into the structure. With this increased technical system complexity comes increased compliance complexity, Nichols & Preston (2000, p.54). The manufacturing process equipment and building interface can also be complex in design, installation and validation. The detail and scope of a validation exercise will therefore be directly related to the complexity of the building and systems and the critical nature of these systems with respect to the quality of the final product.

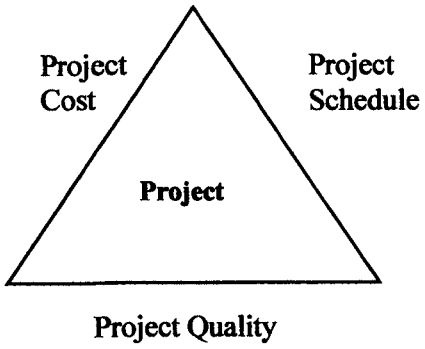
Pharmaceutical buildings house a large number of automated systems. Wingate (1997, p.7) suggests that technological progress has typically increased complexity of automation systems whilst reducing their cost, which makes their use more common and justifiable.
Increased complexity of automated systems heightens the chance of deficient operation. For this reason the regulatory authorities place great emphasis on the validation of computer systems that are used to monitor and control drug production.

3.9 Partnering

Leach (1990) observes that facility construction projects are a balance of the three some times conflicting objectives of cost, schedule and quality. The focus on facility quality and the attainment of those requirements is often the driving objective of the project.
Control of project cost, schedule and quality is suggested by Turner (1986), as being comparable to an equilateral triangle. The triangle encloses the project system and

any changes to either side of the system boundary will change the shape of the system. See Figure 3.6.

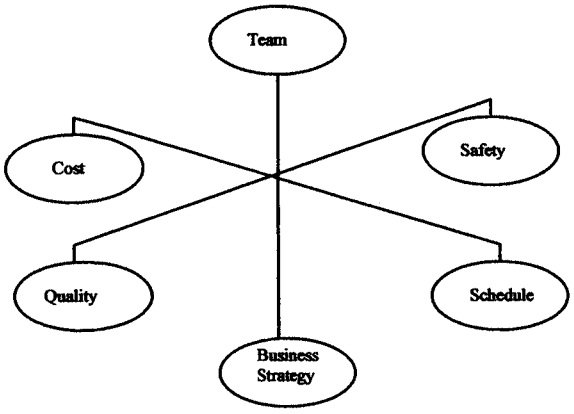
Figure 3.6: Control Triangle (Turner 1986)



Turners control triangle indicates that project quality is influenced by the main variables of cost and schedule (time). This rather simplistic model suggests that project quality can be measured or that project variables (cost and time) impact on project compliance issues.

Southerland (2000, p.16) notes that Turners model indicates that if the construction schedule is reduced the project would incur more expense and/or lesser quality. He goes on to suggest that construction managers, engineers and trade contractors have made many steps forward in the last twenty years to develop methods which do not sacrifice cost or quality. Southerland's expansive model, see figure 3.7, incorporates a broader team focus such as safety and business strategy. The model acknowledges the wide ranging number of project participants that are required to be actively involved in the process of facility construction.

Figure 3.7: Expansive Model of Project Drivers for a Pharmaceutical Facility (Southerland, 2000)



3.10 Implementation - Control and Sequence

The way in which the validation process is enforced on industry is noted by James (1998, p.72) as being back to front. He suggests that validation is imposed on the building user then in turn on the construction organization, engineer and designer. An affect of this is that all parties involved are not sure of the ground rules. James goes on to say that;

> the conclusion often drawn by many experienced people in the construction and contracting industry is that 'they have been doing their job fine until now and all this validation lark is just a load of paper work and a waste of money'.

A number of models have been produced that show the specific sequence of implementation of validation activities. They are the ISPE V model, ISPE (2001) and the Project Activity Model (PAM) model of system documentation by Christoffersen & Jespersen (2003). Neither model clearly indicates to the construction industry their specific role and position within the project environment. The models indicate sequence but in the case of the PAM model do not show the design qualification stage. Terminology utilized is uncommon to the construction sector and a high level of previous pharmaceutical experience is required to understand the concepts.

3.11 Change Control

An important element of a quality assurance system is the requirement to capture and document changes during and after construction of the facility. European commission (2001) Annex 15 states that;

> all changes that may affect product quality or reproducibility of the process should be formally requested, documented and accepted. The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis. The need for, and extent of, re-qualification and re-validation should be determined.

As Gorges (1981, p.24) terms it, validation change control is an 'insurance policy' designed to ensure that systems are not discredited or compromised by improper maintenance or changes. The affect of changes on a system can render the documented validation process worthless. If additions or modifications are implemented without the knowledge and approval of the client's department responsible for change control the facility document package may be at risk of being incorrect and if discovered during a regulatory audit, could have serious implications on site production.

Tashijan (2000, p.8) has highlighted projects fail because unforeseen regulations may cause the need to re-engineer and revalidate systems that are not analysed in sufficient depth. Tashijan also suggests that validation is perceived as a very time consuming activity that is prolonged due to change orders caused by the pharmaceutical client's production requirements.
The concept of *redundant testing,* discussed by Christoffersen & Jespersen (2003, p.12), can occur if a component or set of components exist as a sub-system to a larger system that also requires validation. Both systems may be subject to tests by different groups involved in the construction and installation process. If communications are not clear between the two installing groups the components may be subject to wasteful retesting.

3.12 Quality - Critical Systems and Regulatory Compliance

Regulatory guidelines governing the validation of pharmaceutical facilities tend to give a general view of regulatory requirements. James (1998, p.73) summarizes one of the main perceived regulatory problems as;

there is not a set of rules or national standards nor is there a book on 'how to' which if followed exactly would guarantee that product, plant and production methods would be acceptable. Validation is a philosophy which is amplified by a set of guidelines which are subject to application by the producing organisation and review by its QA department and the regulatory authorities. This approach dismays many engineers and scientists used to a system of standards since it is felt without properly defined rules and regulations to follow the objective is not guaranteed.

3.13 Testing Errors, Faults and Failures (EFF)

Roper (1994, p.16), discusses the concept of testing errors, faults and failures (EFF) in the computer software testing industry which in turn highlights one of the reasons why validation testing can often fail to achieve the pre-determined acceptance criteria. When developing software or designing a facility, individuals make errors, these errors may become faults in the software or facility design which then manifest themselves as failures when the software or facility system is set into operation.
A failure is classed as a deviation or observed departure from the specified behaviour of the system and can rage from catastrophic to unimportant. People make errors and a single error could lead to many faults. A simple misunderstanding at the design stage can lead to the system having many widely scattered faults. The earlier the misunderstanding or error is made the larger is the potential for widely spread faults. The appearance of failure may be a great distance away from the original fault and the failure may only be observed at a later stage of the project life cycle.
Pharmaceutical Facilities can therefore be seen as being potentially inherently unstable until commissioning and validation testing is undertaken. However, due to the nature of delayed EFF's and the inclusion of an adequate testing input domain, the system may still remain at risk of being unstable.
Oskarsson & Glass, (1996) argue that adherence to a standard does *not* necessarily guarantee a quality software product; the same can also be said for compliance of pharmaceutical buildings.

3.14 Project Termination

The process of validation is one that uncovers differences in the constructed facility to that of the original design. James (1998, p.73) argues that if validation is correctly implemented it will cause irritation to the contractor who's main objective at the final stages of the project is to receive payment and leave site. James notes;

> to be confronted with a mechanism which exposes mistakes in a plant in an overt, witnessed and recorded form, is hard, especially in today's competitive commercial environment where project times and budgets have come under increasing pressure.

The end phase of the project is also one where the construction project manager strives to complete the project as swiftly as possible to meet project cost and schedule objectives. If the majority of validation activities take place in the termination phase then the objectives of the project manager may be obstructed if extra resources are required for which there is no extra budget or scheduled time available. The pharmaceutical client's priorities may change and focus on equipment start-up. Commentators such as Dream & Jester (1997, p.92) acknowledge these differences of focus and suggest that the schedule for commissioning and start-up should be integrated with the schedule for validation.

Meredith & Mantel, (2000, p.541) term the final stage of a project as the *termination phase.* The success of the overlap of the termination phase of the construction project with the validation process phase of pharmaceutical production start-up will be dependant on the termination mode adopted by the project team.
Meredith & Mantel, (2000, p.541) suggests that project termination has three possible outcomes:-

1) The project is *termination by extinction* – This means that the project is completed, it is successful and achieves its goals and the building is accepted and handed over.
2) *Termination by inclusion.* Here the project personnel, property and equipment transfer from the project to the new facility.
3) *Termination by integration* – is generally the same as inclusion but with input of the main contractor. e.g. the main contractor has constructed a complex facility and

therefore is required to instruct and advise the client in its operation and maintenance.

The mode of termination and level of integration are key project success factors. But as mentioned the client's and project team member's objectives appear to be at odds with each other.

3.15 Commissioning

Wheeler (1994, p.48) describes commissioning as "putting something in a fit condition for use and readiness for service". It was found that the FDA has no definition of commissioning nor have they approved it in lieu of validation.

It has been observed that there are differences between the tests carried out by a project commissioning contractor and validation engineer. Skelton, (1998, p.32) highlights that the major differences in the tests the commissioning contractor performs are that tests are not always pre-agreed nor properly documented with individual results reported and witnessed by a person independent to the contractor. It is likely that not all problems will be picked up by a general commissioning test alone, and that the commissioning contractor at this stage may have different priorities and focus to those of the validation team. James, (1998, p.88) emphasized that the documentation produced by the commissioning contractor is not and should not be seen as a substitute for the practice of validation.
Proponents for streamlining commissioning and validation activities, such as (Wheeler, 1994), argue that if the installer or contractor is testing the facility and equipment as it is installed, duplication of testing and documentation should be avoided. This suggests the need for an even more *integrated* approach to projects, the success of which will depend on the ability of those involved to function as an integrated team.

3.16 Summary

There appears to be a number of dominant themes that have emerged from the literature. The main themes are related to understanding of the regulatory environment in which both the client and contractor operate and to the specific problematic areas of validation implementation.

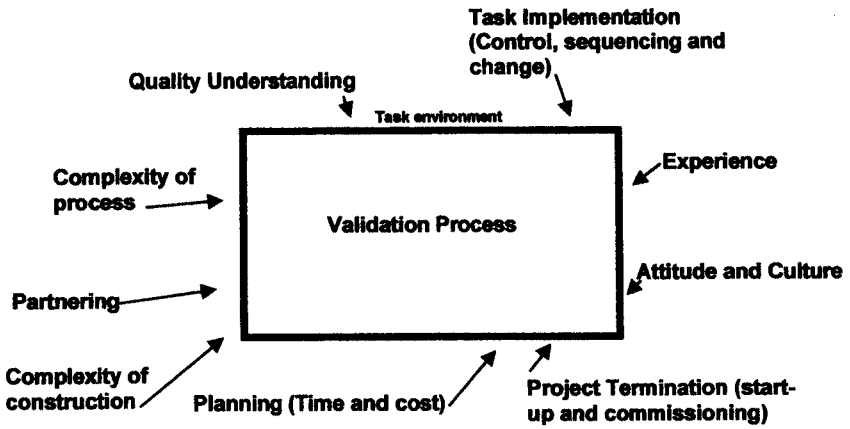
There is a perception that the validation activity is time consuming and costly which appears to be related to the view that the regulations governing the process do not contain sufficient detail and are vague in content.

At the core of the validation process is the installation and operational qualification phases. These phases are of particular importance to the regulatory agencies as they are the final activities before the Performance Qualification (PQ) or the process phase.

The process phase of the project is not the primary focus of this research, as it relates to those areas such as production equipment operation and trial batch production method validation. However, the interface between the process technology and the building cannot be completely ignored. An appreciation of the process technologies utilized and the way in which this knowledge is shared at the final stages of the project is critical in providing the client with a validated facility.

The theoretical problematic areas of validation implementation were highlighted in the literature as planning (time and cost), quality understanding, task implementation (control, sequencing and change), project termination (start-up and commissioning), and complexity and partnering, See figure 3.8.

Figure 3.8: Problematic Areas of Validation Implementation



All of the areas appear to be related by the three key emergent themes of regulatory understanding, experience and as previously discussed in Chapter Two, attitude and culture.

The research has, in the previous chapter, examined both industry views of quality, as a way of establishing differences in the way quality projects are implemented. This chapter has identified the specific theoretical problematic themes which act to hinder the achievement of the project goals.

The study problem phenomenon can be said to be complex i.e. a complex tangle of un-differentiable problems, and because of this, the next chapter, Chapter Four will consider a systems theory approach to this complex problem. Chapter Four will examine systems analysis as a way of providing focus and understanding of the way in which the construction and pharmaceutical industries contribute to the process of validating facilities. The systems approach will then be used to construct a model of the validation process.

Chapter Four: A Systems Model of the Validation of the Construction of Pharmaceutical Facilities

The purpose of this chapter is to apply the concept of systems analysis to the problem of validation in the construction of pharmaceutical manufacturing facilities. Modelling theory and techniques are then examined to generate a systems model of the facility validation process.

4.1 Systems Theory

Checkland & Holwell (1998, p.12) classify systems thinking and methodologies as either *hard* or *soft*. The *hard* system view is one that sees the world as a set of systems that are easily defined, engineered and controlled. Soft systems and methodologies are more applicable to real world problem contexts where the problem is said to be messy or complex.

Pharmaceutical facility construction is generally considered complex due to the process related nature of the building and the associated commissioning and qualification phases required to address the quality requirements of the plant, Odum (1992. p.8).

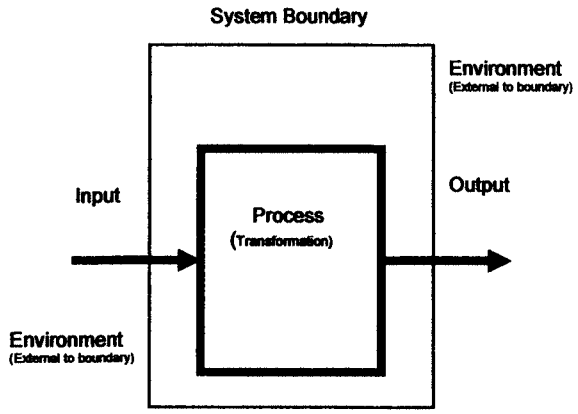
Complex systems can be viewed at manageable levels of abstraction by the application of system analysis, Hicks (1993, p.25). According to Yolles (1999, p.55), systems that are said to be complex, are of the type that are a complex tangle of un-differentiable problems. This is the opposite of problematic situations that can be seen as a set of differentiable problems which are also known as 'difficult' or 'simple'.

Complex systems can be conceptualized by explanation and formulating, which can be used to evaluate how paradigms are able to deal with complex or simple situations. Yolles (1999, p.52), describes this pattern or paradigm of complexity in terms of certainty, softness and structure. The use of system analysis in this study is to produce representations or models of the process under investigation and establish through the adopted terminology a description of the phenomenon. The goal is to

develop a model that in itself is not overly complex, so that it remains understandable. Writers such as Saeed (1996, p.251) suggest the use of problem-slicing to create understandable models, without disconnecting symbiotic processes in a system that contributes to change.

With reference to figure 4.1 a system and its environment comprise of boundaries, inputs and outputs and processes. The system is defined as a group of interacting, interrelated, or interdependent elements forming a complex whole that operate within a boundary. The system inputs cross the environmental boundary and go through a process or transformation resulting in an output which is released back to the environment.

Figure 4.1: Open System (Yolles, 1999)



4.2 Supra systems and Subsystems

Analysis of systems can often expose systems embedded within systems. The construction industry as a whole can be said to be a *supra system* of an individual construction company. Alternatively, the construction industry can be said to be a system and the individual company a subsystem.

Combinations of subsystems act with each other to alter input and to produce output. There may also be an overlap of these subsystems. This is important to recognize because changes that are made in one system may affect another overlapping subsystem.

The construction of a pharmaceutical building will usually involve two main groupings; the client and the building provider. Both the client and provider organizations can be considered as overlapping systems.

Longer response times and increased communications problems are common in overlapping systems. Lucey (1997, p.36) attributes these problems to additional coordination of activities and the requirement to obtain a great number of approvals for change. Organizations with a substantial number of overlapping systems will be less flexible to high-speed change.
The five types of subsystems that are found in organizations are presented in figure 4.2.

Figure 4.2: Subsystem Classification (Lucey, 1997)

Subsystem Type	Function
Managerial	Control, co-ordinate, plan, decisions.
Adaptive	Future consideration. New markets, products and methods.
Production or Technical	Basic organizational tasks.
Maintenance	Provision of rules, rewards and roles.
Supportive	Maintain production subsystem and external environment relationship.

The number of subsystems interconnections can be great and cause difficulties. The process of *decoupling* is used to gain subsystem independence. This independence allows organizations to react to unpredicted instability.
Large organizations such as pharmaceutical manufactures typically consist of a large number of sub-systems of the types identified in figure 4.2.

4.3 Environments

An environment encircles the system and is external to the system boundary. The effect of the environment on the system will influence the process of the enclosed system. The system boundary is described by Yolles (1999, p.13) as permeable to influences from the environment. Whilst Turban (1995, p.40), notes that the environment has an impact on the performance of the system and the ability of the system to meet it objectives, Lucey (1997, p.33), describes the environment as diverse and rarely static.

Environments are viewed in two ways; as *general* environments, such as culture or legal systems and as *task* environments, where all external organizations and conditions directly relate with the systems main processes and technologies. Two systems of client and provider have been established and both systems can be said to overlap. Each system is surrounded by its own environment; the client by the pharmaceutical industry environment and the provider by the construction industry environment. General and task environments enclose each separate system and where the two systems interface a new system task environment emerges, which encircles the project.

4.4 System Boundaries

The boundary of the system is the imaginary line separating the environment from the system. The importance of the boundary is that it defines the system. The boundary encircling the task environment of the project provides definition of the validation process system. Churchman (1975) poses two questions to determine if an entity sits within the boundary of a system: 1) can the systems analyst do anything about the entity in question? and 2) is the object important to the objectives of the system? In terms of defining the validation process as a system the answers to both these questions would both be yes and according to Churchman the entity is within the boundary of the system.

Boundaries can also shift in reaction to factors such as social or organisational change. The effect of the moving boundary will be to alter the enclosed system and systems interface.

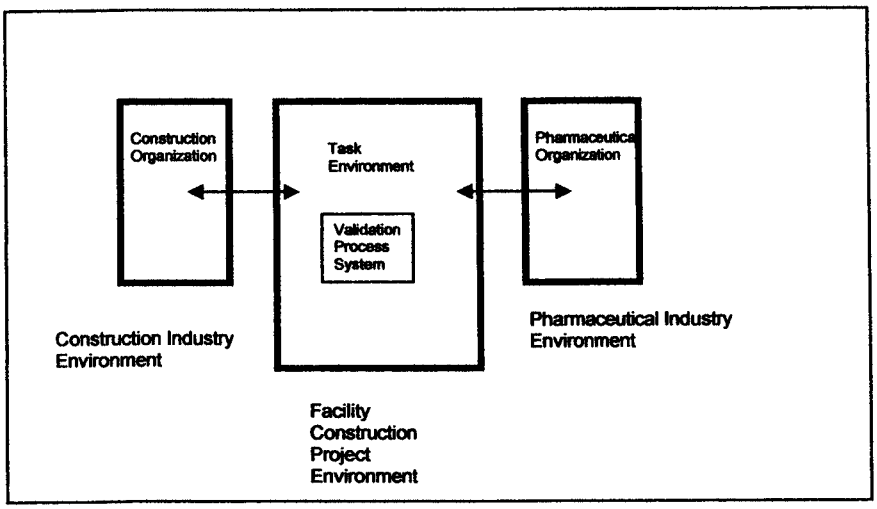
4.5 System Interfaces

The system interface is the area between the boundaries of the system and is the transport medium for the exchange between systems outputs and inputs. In pharmaceutical facility construction projects the construction project and client manufacturing operations are systems. Both systems will interface in the project task environment. The validation process system could therefore be considered to interface with both the construction and client environments in the project task environment.

With reference to the model of analytical classification (2.1) presented in chapter two, the model shows the two client and provider environments and the project

environment. The analytical model can be modified in light of establishing and positioning the validation process system. See Figure 4.3.

Figure 4.3: Modified Analytical Classification Model



Problems occur at interfaces that are not operational. Wetherbe & Vitalari (1994, p.27) describe how the outputs of one subsystem must be suitable for acceptance by another subsystem. This interface is improved by standardisation or adaptation techniques to allow more flexibility when interfacing two systems or subsystems. Adapting interfaces are categorised by Wetherbe & Vitalari (1994, p.31) as *translation* and *slack systems*. Figure 4.3 shows overlapping interfaces between the task environment and surrounding environments. In chapters two and three commentators noted that problematic implementation was related to cultural differences and lack of understanding of the clients validation process system on the part of the construction organization. Limited adaptation and standardization at system interfaces was noted by James (1998, p.74) who suggested that there was a lack of common language between groups.

Another interfacing problem occurs due to the inability of one system to provide outputs at a rate that allows optimal performance of the following system. Poor interfacing because of limited inputs from one system to the other will reduce the operation of the downstream system.

4.6 Transformation

The analysis of all possible inputs and resultant outputs of a certain phenomena would be greatly time consuming and almost impossible. Procedures adopted by systems commentators such as Lucey (1997, p.30) recommend that analysis procedures be adopted to focus on outputs that are central to the system objectives and to select inputs for examination and control which have major effects on the outputs. This indicates a hierarchical analysis as a way of forming a systems model. The disadvantage with analysis of only system inputs and outputs would be that the system would be seen as a *black box.* The study of the validation process is predominantly concerned with transformation and therefore needs to follow a suitable systems analysis procedure to allow model development.

4.7 System Types

4.7.1 Black Box Systems

Systems that are classified as complex may have processes that are too difficult to describe or structures that are unfamiliar or unknown. As Yolles (1999, p.13) suggests, the ability to comprehend or manage such systems may not be possible. In certain instances black box analysis is applied rather than an attempt to describe the transformation process of the system. The system is therefore only described in terms of its inputs and outputs. Analysis of this kind will only allow a comparison of output to input. It acknowledges that a transformation process has occurred, but without knowing or understanding the workings or functions of the particular process.

The black box concept allows system analysts to study complex systems based on the application of assumptions that:

1) The individual black box processes are independent.
2) Stability exists in the processes.

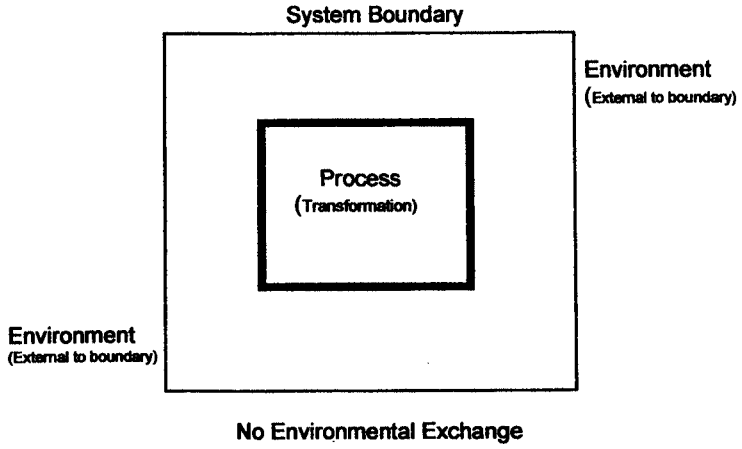
This concept is used by those attempting to understand the processes of complex systems where a depiction of the high level process is sought, followed by a detailed analysis to develop a detailed understanding.

4.7.2 Open and Closed Systems

Hicks (1993, p.31) distinguishes that closed systems are assumed not to react with the environment whilst open systems allow inputs from the environment. The adoption of a closed system view is used as a simplification because as Hicks (1993, p.31) states 'all systems are open to some degree'.

Closed systems are stable and mechanistic and are often self-contained. Interactions with the surrounding environment are uncommon. The system is stable and predictable, however, if a system has no environmental input it will decay or deteriorate. New inputs such as energy and information are required for the closed system to continue to operate in the long term. Closed systems are time dependant and commonly function as a purely closed system for a short term. A model of a closed system is given in figure 4.4

Figure 4.4: Closed System (Yolles, 1999)



The open system concept was developed from the work of von Bertalanffy (1956) and was originally developed in the area of biology.

The open system, when accepting inputs and passing outputs, reacts with its environment. Social organisations are classed as open and are subjected to changes in the environment. Adaptation to environmental change within open systems is central to organizational success and survival. The degree to which adaptation takes place is considered by Warboys *et al* (1999), who suggest that organizations are not open to all environmental stimuli and respond only to stimuli they have the structure to recognise.

The adaptability of a system to changes can also be seen as a measure of operational success. An organization that has a suitable, flexible, internal structure and willingness to change must also have a management structure that is capable of implementation.

Kagioglou *et al* (2001, p.85), in a study of performance management in the construction industry, offer the open system concept of output measurement from the construction process as a way of developing a performance measurement process conceptual framework for transferring best practice into construction.

4.8 Socio-technical Systems

Kingdon (1973, p54) notes that socio-technical systems are a type of open system viewed in terms of their technology and social relationships. He points out that system processes can be affected by the level of technology and the knowledge of this particular technology. Such effects have been highlighted by Nichols & Preston (2000, p.54).

4.9 System Inputs and Outputs

System inputs move from the environment through the system boundary to the transformation process. System outputs have been described by Turban (1995, p.39), as finished products or consequences of being in the system. Inputs and outputs take many different forms and can be, for example, data, raw materials, people, resources, performance, consequences or services etc. The transformations of inputs into outputs are known as *purposive* processes.

The validation processes systems appear not to have predictable inputs and outputs and are therefore not stable or mechanistic. If inputs and outputs are unclear or unpredictable the system has to become adaptive to cope with these uncertainties.

Systems that are held together with a common purpose are said to be *synergistic*. The reduction in system synergy will give rise to an increase in subsystem interdependence. As Yolles (1999, p.18), comments, that this individual goal focused behaviour may be 'contrary to the purposes of the system as a whole'. This synergistic system behaviour will be analysed later in the study.

So far in this chapter, facility validation has been described in terms of system analysis terminology. By relating the process and surrounding environments the position of the task environment was established within the analytical model. The previous chapters have identified problematic themes associated with process implementation. The focus now shifts to establishing a model that acknowledges these problematic themes by providing sensing, comparison and feedback mechanisms as a means of control.

4.10 Control and Cybernetics

The cybernetic concept is based on the co-ordination of the human brain and nervous system to achieve control actions. Information has to be gathered, processed, communicated and applied to the system. System order is then maintained through feedback.

Cybernetics has, in the past, been confused with artificial intelligence. Oliver & Roos (2000, p.125) note that it has evolved from a shared agreement about meaning and information is an attribute of an interaction rather than a pre-set action.

The ability to control depends on application of control at discrete phases in the project. The validation process model will need to address the actual points of control measurement and identify deviations and corrective actions.

To modify system output a control system will be required. System control is typically achieved through the application of three basic control theories; *cybernetic, go/no-go* control and *post* control. The control normally takes the form of a *feedback* process. If a system does not possess a feedback function for regulation the system cannot adapt to changes.

The feedback process allows the output of the system to be measured against a standard. The resultant difference between the output and the standard is corrected by adjusting the input.

Ashby's Law of Requisite Variety, Ashby (1956), relates to system control in that it states;

> to control a system there must be available a number of countermeasures equal to the variety displayed by the output of the system.

This means that in large organizations simple control systems will not control the multi-department company. At best simple control systems will only be effective in narrow areas of the organization's scope of operations. A criticism of Ashby's law, is that to achieve full control by having an equal number of countermeasures, would require the control system to understand and react to an unexpected variety of outputs.

Koontz & Weihrich (1988, p. 495), suggest a control cycle of eight requirements for effective feedback control:

1. Actual performance
2. Measurement of actual performance.
3. Comparison of actual performance against standards.
4. Identification of deviations.
5. Analysis of causes of deviations.
6. Program of corrective action.
7. Implementation of corrections.
8. Desired performance.

Control or action within a system is achieved by the process of cybernetics. Weiner (1948), a mathematician, derived the term from the Greek word meaning 'steersman', (kubernts which means governor). Cybernetics is a discipline that has its origins in electrical engineering, biology, mathematics, anthropology, psychology and neurophysiology. Early applications included the control of systems such as electrical circuits and simple robots. The initial area of use was within engineering based systems, but the relevance to the softer sciences and social systems was clear from the beginning.
The cybernetic process involves good control and communications. Koontz & Weihrich (1988) consider the purpose of communications within an organization is 'to effect change and to influence action in the direction of the corporation's overall interest'.

Control involves the establishment of standards against which the actual performance is measured. In the same way the validation protocol establishes tests which are measured against the protocol writer's understanding of regulations. In chapter three,

Wood (2001, p.51) argued that the clarity in the current GMP regulations is a factor that has lead to excessive validation and increased costs.

A form of corrective action is made to achieve the planned goal.
Yolles (1999, p. 14) recommends that the measurement of deviation should be on a future basis, so to allow the detection in advance of occurrence and to allow *corrective actions* to be implemented.
The control and feedback loop of a cybernetic system consist of a *sensor, comparator* and *effector*. The system sensor measures or records the system deviation. In an organization the sensor recording will be in the form of paperwork.
Lucey (1997) recommends that the sensor should:

1. Be appropriate for the system.
2. Be sufficiently accurate.
3. Timely.
4. Be free from bias.

The comparator is included in the system to compare the actual results with the standards required and the effector is the function in the organization that reacts to the results of the comparator. If the comparator sees a variance an appropriate action is issued to make a system adjustment. The comparator function compares output with predetermined standards and the effector or *Decision Maker* determines if the measured difference is of a sufficient size to require correction. If an action is required, the effector acts to alter the process or input to produce resultant outputs that conform more closely to the comparison standard.

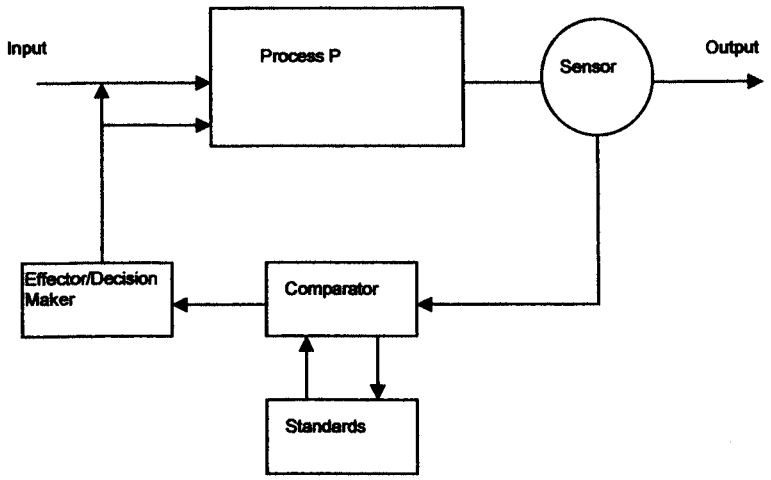
It is suggested that, within a validation process system, the system sensing function, comparator and effector or decision making function would be that of the protocol executor. The instrument used to control system output would be protocol testing documentation.

The purpose of cybernetic or negative feedback loop system, as it is sometimes termed, is to attempt to decrease the deviation from the standard. When a system output deviation increases away from the standard, the control system must react in the opposite direction. Control action is generally proportional to the deviation.

Lucey (1997, p.33) comments that the way in which the difference between output and the standard is addressed is dependent on the nature of the operating system and the controller design.

Cybernetic control systems can said to be first, second or third order. The first order system shown in figure 4.5 is a simple model that is goal seeking.

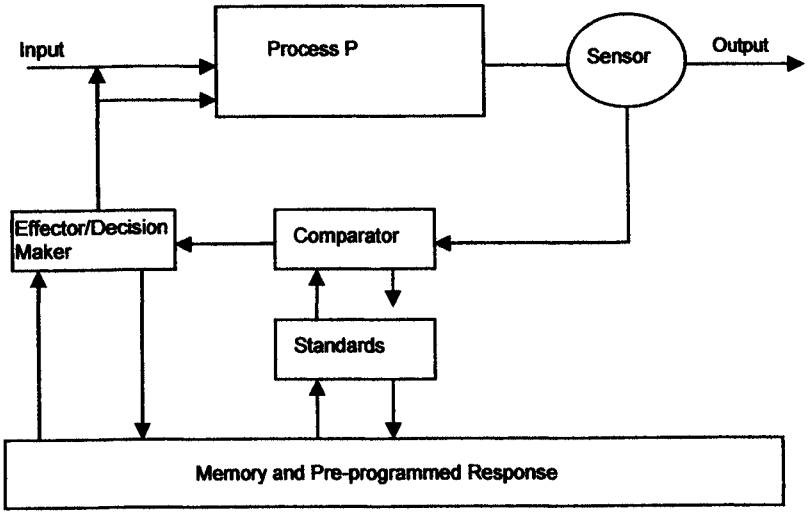
Figure 4.5: First Order Cybernetic Systems Model (Weiner (1948)



An example of a first order system model is a room humidity stat, where humidity is the set standard of the system that is maintained by the environmental control system. A problem with the control of this type of first order system is once the standard is set there is no way of altering the goal, except by intervention from outside the system.

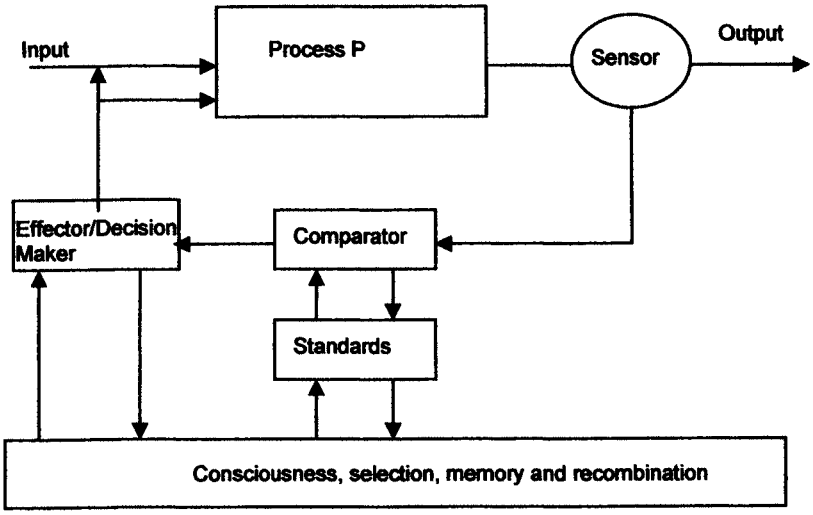
Figure 4.6 shows a second order model. Here the goal can be modified by adjusting the system standard. The use of a program or pre-set functions can allow different levels of standards to be maintained. The modification of the first order cybernetic humidity stat example, to include a programmable controller to allow different system standards of humidity to be set would represent a second order cybernetic system model. The use of pre-programmed system standards will allow goal changing to occur. Second order systems do not have the ability to make conscious decisions as they only contain pre-determined reactions to change.

Figure 4.6: Second Order Cybernetic Systems Model (Weiner 1948)



In third order systems (see figure 4.7) goals can be changed without specific preprogramming of the system standards and can reflect on system performance and decide in ways that are not contained in its instructions. They also have reflective consciousness and must contain humans. An advantage of third order systems are that they can deal with the unforeseen or unexpected. A disadvantage of this system type is that they can lack reliability and predictability which can often be associated with making objectively rational decisions.

Figure 4.7: Third Order Cybernetic Systems Model (Weiner 1948)



The third order model represents more accurately, than the first and second order models, the validation process system, as it contains the human element of reflective consciousness and the components to effect change (Weiner, 1948).

The cost of implementation of control can be expensive in terms of resources and time. Lucey (1997, p.153) recommends that the concentration of control effort should be focused on those areas that are *vital* in the fulfilment of overall objectives.

It is proposed to model the validation process system on the principles of the cybernetic third order model. However, before this can be achieved the modelling process requires examination.

4.11 Systems Modelling of the Validation Process

To model a situation a view of reality has to be formed which allows us to formulate explanations of the phenomena being studied.
An attempt is made to reduce that system complexity with the goal of providing explanations and descriptions.

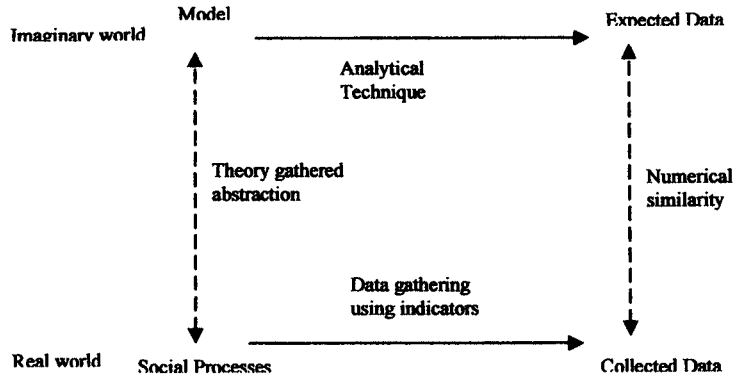
According to Veryard (1992, p.12), models can be used for the following purposes:

1. Scientific theory or hypothesis.
2. Abstraction (based on classification, aggregation and or generalisation).
3. Objective description of a business system.
4. Plan/map/orientation.
5. Architecture, pattern language, blueprint or template.
6. Statement of business intentions and or perspective.

To construct a *valid* systems model, Veryard (1992, p.15), recommends that the model must clearly indicate the focus or area of the problem being modelled. It must identify and explain the system attributes, entities and connections and the model must explain the specific reason for production, its influences and future uses.

The proposed model of the validation process system is based on theoretical knowledge and insights about the problematic implementation of the process, which has emerged from the review of literature in chapters two and three.
It is a *theoretical* model that is a representation of a set of hypothesis or propositions which are used to explain the connections and interactions between the observed phenomena.
Structural correspondence existing between data and the model is a concept investigated by Gilbert (1981, p.4). If a direct relationship exists between the data and the model then he suggests that the relationship is said to show structural correspondence.
The meaning of this correspondence is that it has been proved, in the reality of the perceived phenomenon, the model may exist and can be used to make predictions about how the 'real world' reacts to system changes.

Figure 4.8: Data Model Relationship in Structural Correspondence (Gilbert, 1981)



Gilbert's correspondence model is a simplification which does not consider a robust modelling method including model validation. It is important to recognise the limitations of models, that they are simplified representations of the 'real world' that cannot display all system and environment interactions.

In order to improve on the correspondence model Gilbert (1981, p.6) suggests a number of steps are needed to be taken. They are:

1. Design the model based on prior theoretical knowledge and insights. Ensure that the model sufficiently covers all the relationships considered of high level importance in the problem area to be studied.
2. Decide on the analytical technique that will be used. This decision will determine the model form and data type to be generated.
3. The model and analytic research instrument are used together to generate a set of expected data. This data is in the form of a number of theoretical propositions.
4. The actual data obtained through the analytic technique is compared with the expected data.
5. The degree to which the results vary verify the acceptability or otherwise of the model.

4.12 Model Validation

The model will be assessed by a number of tests rather than one single test. Forrester & Senge (1996, p.209) recognised that constructing model confidence is best achieved by multiple tests. The test data will be used to compare the model and the empirical reality of the observed phenomena. The first model test will be utilized as a *pilot* study. The model will then be validated, by testing it with other independent sets of data from case studies and an industry survey.

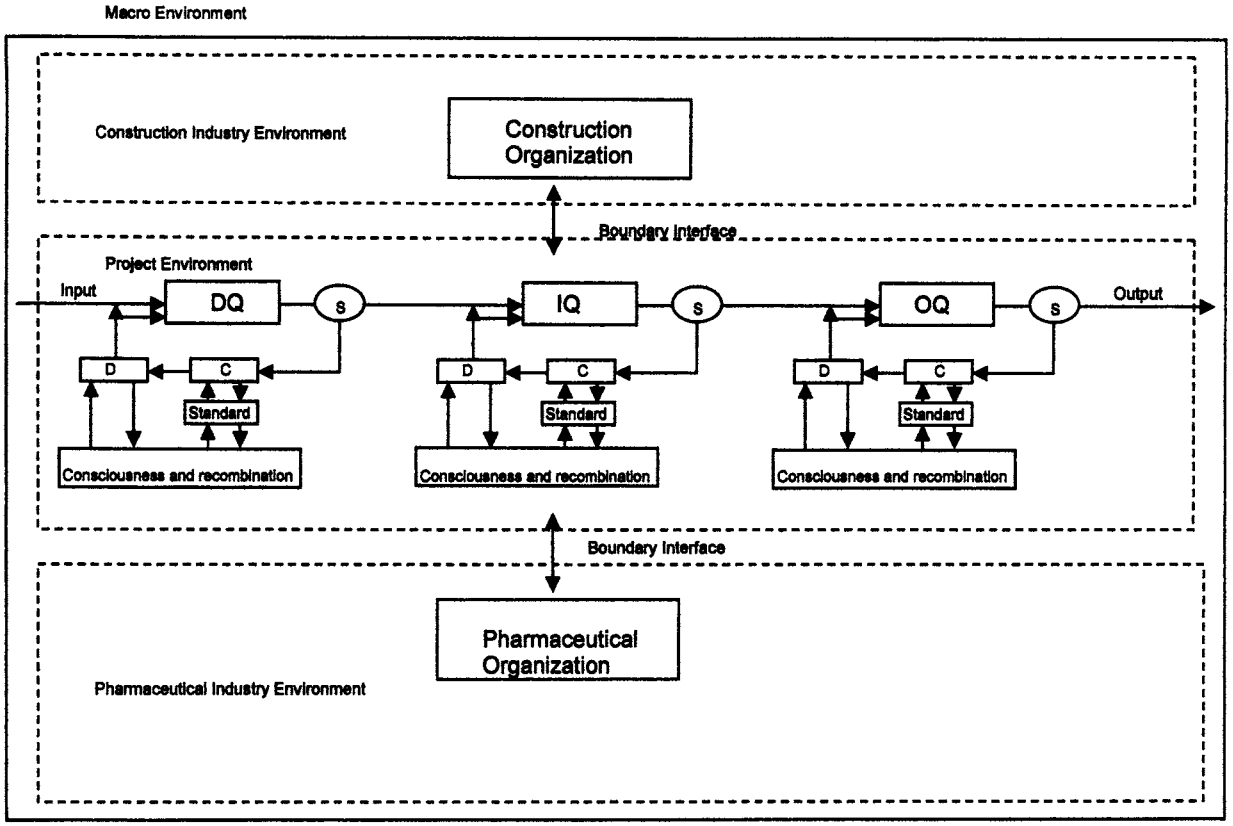
4.13 The Research Propositions and Proposed Model

As a result of the literature review in previous chapters, the examination of systems analysis and identification of a set of problematic implementation themes now makes it is possible to construct a model of the validation process. See figure 4.9.

The single third order model is adapted to include the main areas of research concern i.e. design, installation (construction) and operation. This has been achieved by presenting the sub-systems of DQ, IQ and OQ in a time series manner which will allow the analytical process that Yin (1994, p.106) refers to as pattern matching, later in the research. The model is encircled by the macro environment and surrounds both the construction and pharmaceutical environments which interface in the project or task environment.

The validation process system consists of a series of inputs, outputs and process transformations that *should* occur to cybernetically control the goal seeking process. Sensing and feedback are achieved by collective operations within the task environment.

Figure 4.9: Third Order Validation Cybernetic Model



Key – S = Sensor, C = Comparator, D = Decision maker

The research propositions are presented as follows;

The first proposition, and potentially of major significance to the study outcome, is based on the effects of the negative association between the current regulations governing the validation process and the interpretation and implementation of the regulations.

P1: *System regulatory inputs are implicit and can result in embedded non-compliance affecting the validated status of the facility and its building systems. Regulations are implied though not directly expressed and in effect cause GMP non-conformances.*

The literature review uncovered that the current GMP regulations appear to be vague and can result in expensive excessive validation. Research into the similar, highly regulated industry of computer software testing provided the concept of errors, faults and failures (EFF). This concept may also be present within the task environment of the research study and may be linked to the project teams understanding of the validation process regulations.

The next proposition builds upon proposition P1 and suggests that a project team structure that is derived from both industry environments and acts in the task environment should be adequate in terms of resources, planning, communications, integration, and skill levels. The project team structure should therefore include construction project managers, Heating, Ventilation and Air Conditioning (HVAC) engineers, calibration engineers, validation engineers, quality assurance experts, plant and maintenance engineers and all relevant client user groups.

It is therefore proposed that;

P2: *The structure of the project team should be appropriate to the task environment.*

The literature has also uncovered, mainly through a review of pharmaceutical related literature, that there is an industry perception that the implementation of the

validation process is lacking[1] and could be improved. The derived cybernetic model of the validation process system incorporates those features that have been identified in the literature as being capable of goal steering and system control. This yields the following proposition;

P3: *In order to maximise the potential success of the project the validation process should be controlled through feedback and sequencing of implementation tasks.*

Turning to system complexity, the literature reveals that pharmaceutical facilities contain a high level of automated processes and are highly serviced to provide *clean* spaces. The literature also indicates that there is a positive association between validation cost and system complexity which is at variance with the reducing cost of complexity, noted by Wingate (1997). This then leads to the fourth proposition that;

P4: *The complexity of the validation testing procedures should be appropriate to the complexity of the systems in the task environment.*

The final proposition establishes the view, suggested in chapters two and three, that there are differing views of quality within both industry environments. The evidence of a culture clash and lack of common language between project team groups leads to the proposition that;

P5: *The desired system output, that of regulatory compliance, is affected by differing views of quality.*

[1] See Chapter 3, Figure 3.8: Problematic Areas of Validation Implementation.

4.14 Summary of Research Propositions

The following summary table represents the key theoretical problematic areas of validation, discovered from analysis of current literature and connects each theme to the study propositions that will be used to guide the research process.

Figure 4.10: Study Propositions Summary

Proposition	Theoretical Validation Themes
P1: System regulatory inputs are implicit and can result in embedded non-compliance affecting the validated status of the facility and its building systems. Regulations are implied though not directly expressed and in effect cause GMP non-conformances.	Quality understanding, experience.
P2: The structure of the project team should be appropriate to the task environment	Planning (time and cost), communication, integration, resource.
P3: In order to maximise the potential success of the project the validation process should be controlled through feedback and sequencing of implementation tasks.	Task implementation, control, sequencing and change, partnering.
P4: The complexity of the validation testing procedures should be appropriate to the complexity of the systems in the task environment.	Complexity, project termination (start-up and commissioning).
P5: The desired system output, that of regulatory compliance, is affected by differing views of quality	Culture and attitude, Quality understanding, experience.

Chapter Four has successfully applied systems theory to the research problem to develop a steering model for the validation process.

The next phase in the study is to examine the theoretical propositions and model within a *real* world or task environment, as opposed to the imaginary world of theoretical concepts. This will determine if a relationship exists between the collected data and the model, to prove or disprove structural correspondence.

Before this can be achieved, an examination of research strategies and methodologies must be undertaken to provide a platform for collecting and analyzing information. This is presented in Chapter Five.

Chapter Five: Research Methodology

This chapter considers the research strategies that could be used to achieve the objectives set out in chapter one. The chosen research strategy will be described and justified. The unit of analysis and sources of data will be identified along with the instruments of data collection.

Limitations of methodology, internal and external validity and ethical considerations will be covered.

The chapter is based around the following topics of research strategy options, sampling procedure (data collection), procedure of observation and data analysis.

5.1 Research Strategies

Two main research strategies identified by Glaser and Strauss, (1967) are verification and generation. Verification, positivist or logico-deductive strategies relate to proposition or hypothesis testing, which is most commonly associated with empirical data that is quantitative (See Easterby -Smith *et al,* 1991).

Generation or interpretivist methods of research rely on allowing theory to emerge from the collected data (See Bryman, 1988).

Traditional quantitative research can be viewed as a linear process (Flick, 2002, p.40), where a model can be constructed prior to entering the field of study. This model is based on theoretical propositions derived from earlier empirical findings, literature, or pure theory. From this, hypotheses are derived and tested. This method is regarded by some researchers as being too 'concrete' and focuses only on the pre-conceived theoretical propositions (Flick, 2002, p.40).

A common problem, described by Travers (2001, p.41) is that researchers make and bring epistemological assumptions to the process of research. These views, often subconscious, influence the understanding and interpretation of gathered qualitative data. Proponents of positive ethnography research such as Hammersley (1990, p.9), agree that studies should be judged by (a set of) scientific criteria including representativness and reliability. There is also a view that studies involving human observation must conform to physical science methodology and that strategies such

as case study participant observation are sometimes regarded as non-scientific (Easthope, 1974, p.19).

Easthope summarises the essential differences, see figure 5.1

Figure 5.1: Qualitative and Quantitative Research (Easthope, 1974)

Qualitative Research	**Quantitative research**
Research Problem How, Why?	**Research Problem** Who (how many)? What (How much)?
Literature Review Exploratory – what are the variables involved? Constructs are messy - Research questions are developed.	**Literature Review** Explanatory – what are the relationships between the variables which have been previously identified and measured? Hypotheses are developed
Paradigm Critical realism/interpretive	**Paradigm** Positivist
Methodology For example, case study research or action research	**Methodology** For example, survey or experiment

Interpretivists believe that the collection of large data sets encourages a positive mindset when analysing data such as that collected from an interview. The distinction between the interpretivist and positivist perspective is that the positive study would make data comparisons by measurement of variables in different settings to develop a theory. The interprevist approach would be to conduct an in depth study in one social setting to gain knowledge rather than comparative studies based on spending smaller periods in a number of sites.

5.2 Qualitative Research

Qualitative methodologies deviate from scientific paradigms which are structured around rationalism and positivism. Qualitative research is typically characterized by methodologies such as observation, discourse analysis, interviewing, ethnographic fieldwork and textural analysis, (Travers, 2001). It involves the description of the data obtained by researchers in their contact with the situation studied. Thus, process is more emphasized than product and the researcher's interest will be linked to

subjective aspects of human behavior, understanding of the meaning of events and social interactions that happen in daily life.

5.3 Study Logic and Research Design

Research designs are classified by Trochim (2005) as randomized or true experiments, quasi-experiments or non-experiments. Experimental designs are considered as the most rigorous by some and generally rely on the idea of probability.

It is suggested by Trochim (2005) that experimental designs are intrusive and not suited to most 'real world' contexts. The context of an experiment is often an artificial situation that is utilized to assess causal relationships. In social research, experiments will produce high internal validity because of the structured experimental environment. In 'real' contexts this experimental environment may differ from the 'real' one and generalizations would be affected by external validity. Quasi-experimental designs take the form of *nonequivalent, dependant variables design* and *regression-discontinuity design.* Nonequivalent, dependant variables designs are based on pre and post tests for treated and comparison groups. Here the groups are not created by probability. Regression–discontinuity (RD) designs are characterized by assignment to treatment using a cut-off score on a pre-treatment variable i.e. a methodological approach to determine the effectiveness of a program or treatment. Statistically RD designs are not as powerful as experimental designs.

Non-experimental designs, in their simplest forms can consist of a 'one-off' survey design with a single observation. Designs of this type, when considering certain types of questions, are noted by Trochim (2005) as 'strong' designs.
Types of questions that exist in non-experimental designs are discussed by Yin (1994), who notes that 'how' and 'why' forms of research question are commonly asked. The type of question posed will have an influence on the type of research strategy used. 'How' and 'why' questions relate to explanation, strategies such as case studies, histories and experiments. Both experimental and case study strategies focus on contemporary events. The essential difference between experimental and

case study strategies is that experiments will require control over social behavior, which in the context of this study is not possible.

According to Myers (1997) the term "case study" can be used to mean a unit of analysis or a research method. As a research method, the case study is empirical, in that it relies on or is derived from *observation.* The case study, as an empirical methodology, is guided by observation, not theory, and should be verifiable or provable.
Yin (2003, p. 6) notes that case studies are an empirical inquiry 'where the goal is to discover theory by directly observing a social phenomenon in its raw form'.

Gephart (1999) states that there are three main research paradigms; positivist, interpretivist and critical (post-modernist). In the same way case studies can fall into these categories. The adopted paradigm is argued by Myers (1997), to depend on the 'underlying philosophical assumptions of the researcher'.

Case studies can therefore be descriptive, exploratory or explanatory, each method with its own advocates. Pare (2001), in his research into information systems, used both exploratory (theory building) and explanatory (theory testing) methods. Here a mixed-mode strategy was used in two exploratory or positivist studies combining two approaches in each of the studies. The first approach consisted of selecting and grouping concepts and relations. This approach enables the researcher to see the major concepts simultaneously in their relationships to one another. The second approach involves freeing the researcher from constraints of existing theory with the purpose of developing concepts, hypotheses and relevant theory.

Mix mode research of this type is at odds with supporters of theory-building research. Eisenhardt (1989), argues that preordained theoretical perceptions may produce bias that will limit the research outcomes. However, she goes on to concede that it is impossible to carry out research without having first any preconceived theories about the phenomenon.

A mixed mode case study research strategy will be utilized for the main information gathering phase of the research study. The main reasons are summarized as follows:-

1. 'How' and 'Why' questions are predominantly asked.
2. The researcher will have access to behavioral events, but, has no or very limited control over them.
3. Contemporary sources of case study evidence are accessible.
4. The case study strategy allows for the collection of a full range of qualitative information including: interview, memo and observation data.

5.4 Collecting the Data

Having established that the research should follow a predominantly qualitative, rather than quantitative strategy, using case study methodology, specific field study research methods were assessed for their suitability. The following sections discuss the two field data gathering and analysis research techniques that have been adopted in this study. The field research is executed using a method based on a *grounded theory* strategy and the main method of case study data collection is by the method known as *participant observation.* The processes and reasons for selection are discussed below.

5.5 Grounded Theory

The central concept of grounded theory, according to Glaser & Strauss, (1967), is that theory is derived from and grounded in data; where theory generation rather than verification is the ultimate aim. Martin and Turner (1986, p.141) suggest that grounded theory is;

> an inductive, theory discovery methodology that allows the researcher to develop a theoretical account of the general features of a topic while simultaneously grounding the account in empirical observations or data.

The aim of grounded theory according to Dick (2000) is to understand what is happening in the research problem setting and how key people interrelate and manage their activities. The ethnographic methods commonly used in this type of research are observation, conversation and interview. The data collection processes is also supplemented by 'note-taking'. An initial comparison of data sources is made which helps generate theory. Typically the process involves writing the results in the form of code in the margin of the data sheet. This is known as *manual coding* and its objective is to group categories of codes together which share similar themes or variables, properties or sub-categories. Within the social sciences these code

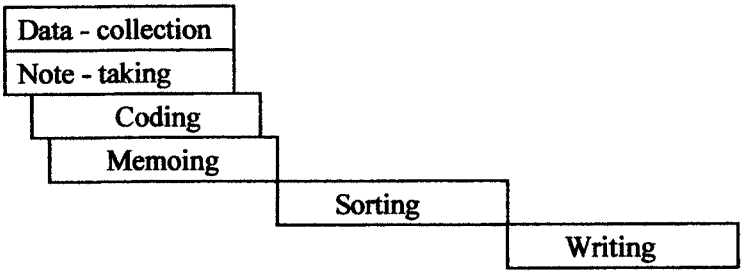
categories are classed as *parent* and *child* codes and can be mapped by a coding family tree.

During the coding process propositions relating to theory are said to occur. Theoretical propositions are the observed relationships that exist, at a level, between family tree codes. Dick (2000) suggests that code categories that relate specifically to the study are central to generation of the emergent theory. As categories and properties emerge, notes or *memos* are used as the method of expressing the newly formed theory. As more data is collected then the amount of memos increase to a point where data *saturation* occurs. At this point in the sub-process called *theoretical sampling,* all possible properties have been examined within the data. This is the stage the memos are *sorted* into similar groupings in a sequenced manner to form a clear view of the theory.

The point at which theoretical saturation occurs is when 'no new or relevant data seems to emerge regarding a category and the relationship between categories are well established and validated' Strauss & Corbin, (1998, p. 212).

Sorted memos provide what Dick (2000) refers to as the 'skeleton' of the research, which provides a clear framework for the final grounded theory stage, that of *writing.* Figure 5.2 shows the process stages of a grounded theory study.

Figure 5.2: Grounded Theory Methodology (Glaser & Strauss 1967)



Research methods of this type have been criticised and theories derived from qualitative data are said to be *impressionistic.* Glaser and Strauss (1967), major contributors to this type of research, recommend that the data should be used in a systematic and rigorous way. A precise description of how theory is generated and its relevance should be recorded. The utilization of systematic canons and rules of

evidence of quantitative analysis are suggested as ways of increasing the validity of the methodology.

The grounded theory method relies on *theory building* or *interpretivism* and not positivist paradigms. The flexibility of grounded theory, as opposed to more rigid research designs, has made its use popular in social and cultural contexts.
A grounded theory–like approach is particularly applicable to this study for the following reasons:-

1. It allows for emergent design. Changes in the structure of the fieldwork organizations can be accommodated in the revised design.
2. Data collection and analysis takes place concurrently allowing a more specific focus as analysis proceeds, hence, offering a steering mechanism to the process.
3. The model of grounded theory is relevant to the social context and the data is derived from every-day perspectives of the participants.
4. The process aligns itself with all sources of qualitative data such as informal conversations and interviews.
5. Grounded theory acts as an analytical tool. As, noted by Bailey, (1997, p.7), emerging categories can be related to existing theories in relevant literature, allowing for the possible evolution of new theoretical findings.

Strauss & Corbin , (1990) agree and suggest that as theory evolves elements of previous theories can be incorporated if they are pertinent to the data gathering phase of the study.
The theoretical literature can then serve as background to which comparisons can be made between findings from actual data gathered in grounded theory studies.

5.6 Sensitizing

As reported by Gephart (1999), the process of grounded theory research often commences with orienting or sensitizing concepts which generate general 'first' ideas about the phenomenon being studied. These initial micro level inspections of

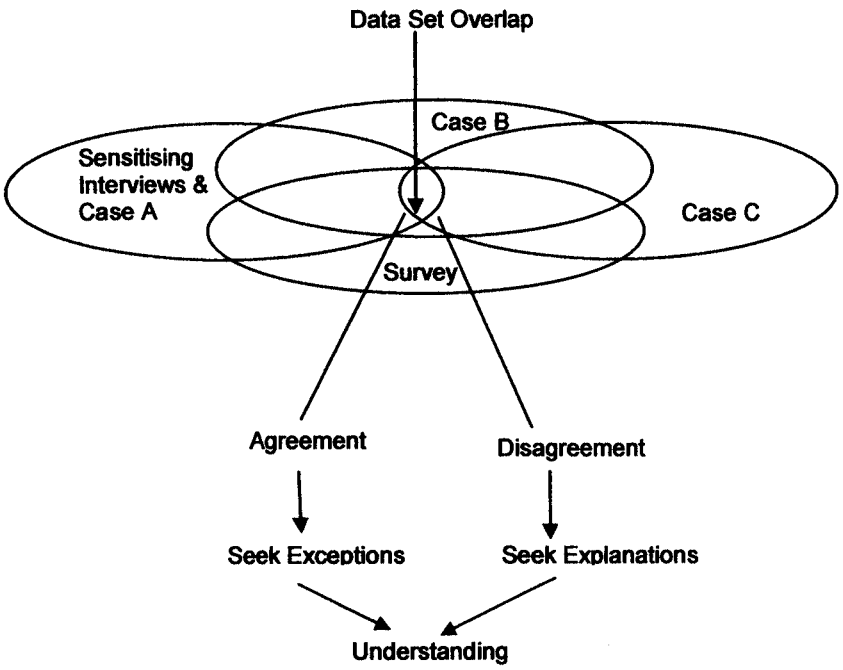
the social setting allow for later elaboration and development of the problem examined.

This study will initially utilize sensitizing for identification of basic category data prior to the main phase of data collection and analysis. Case study A, which will also act as a pilot study, will commence with two interviews with the aim of generating category or themes that will be used to 'build upon' the fieldwork of case study A and subsequent case studies.

The approach to using a grounded theory-like methodology in this study research is based on a model developed by Dick (2000) who successfully used the methodology through interviewing for organizational diagnostics. This technique was based on open ended questions so the data gathered was based on the informants overall experience rather than answers to specific questions. Themes were noted as key-words and the themes from both interviews were then compared. A number of similar themes emerged from this analysis. Probe questions were then asked, in the case of where similar themes emerged, to seek exceptions and in the case of dissimilar themes, to explain differences. As with grounded theory, explanations emerge from the informant's data which results in the generation of theory. This study is based initially on theoretical themes and the generation of themes or categories and the elaboration of these themes to develop theory, through a grounded theory-like methodology.

With reference to figure 5.3.the model is adapted to include additional data sets and an orientation stage.

Figure 5.3: Grounded Theory Model of Data Collection and Analysis. (Adapted from Dick (2000))



The qualitative information from case studies A, B and C will be the sources of primary data. As an element of external validity to the research model, data from a survey is included as the fourth data set.

In the model developed by Dick (2000) information gathering was collected from interviews that were initially open ended in structure. Once key themes had been identified and verified, by cross data set comparison, specific probe questions where asked. In this research study, the information gathering method is a combination of qualitative methods including interviews and observation allowing the researcher to enter the field without 'a priori' themes. This method will permit the generation of categories to emerge from separate data sources of the cases and survey. The key themes of the literature review of chapters two and three, which informed the cybernetic validation model, will be aligned with the field-work data to establish the degree of structural correspondence.

These common themes are represented in figure 5.3 as data set overlap. 'Probe' questions, of the informal type, will be used to seek explanations and exceptions across the data sets. In the same way that probe questions increased focus in the research carried out by Dick (2000), data focus for this research, will be sought by changes and shifts in observation. Data gathering and analysis continued until saturation was achieved.

It has been acknowledged by Kelle (1997), that qualitative research can generate a large amount of unstructured data, like memos, interviews and project documentation. Data management problems are common and cannot easily be solved by standard database systems. A computer software package was selected and utilized to assist management, collection and analysis of the case study information.

5.7 Computer Assisted Qualitative Data Analysis Software (CAQDAS)

Since the mid nineteen eighties software packages such as the Ethnograph, Hyperqual, Winmax, Atlas /ti, Nud*ist, Kwalitan and Hyperresearch, have been developed to assist in the management of qualitative data during the process of analysis.

The software indices, cross references data and text address segments are stored as pointers together with the names of the codes allocated to the text address segments. Retrieval algorithms find and retrieve the segments to which codes are assigned. It is also possible to link one code to another by defining sub-codes thereby resulting in a hierarchical network of codes.

A decade later it was observed that the structure of a theory developed in a qualitative project could be represented through a network of codes.

Barry (1998) suggests that the use of CAQDAS as an analytic data handling tool may:

> Help automate and thus speed up and liven up the coding process; provide a more complex way of looking at the relationships in the data; provide a formal structure for writing and storing memos to develop the analysis; and, aid more conceptual and theoretical thinking about the data.

Seidel (1991) when discussing the software package, the Ethnograph, states that the coding process may have led to users getting so caught up with learning how to code that they might have lost sight of their data. However, Barry (1998) argues that those who have tried the software have realized that it is not possible to analyze data without reading and being familiar with it first.

Codes are derived from common sense concepts and abstract theoretical concepts. Figure 5.4 gives an example of coding.

Figure 5.4: Qualitative Coding

Code Number	Code Description
1	**job and career**
1.1	job and career/aspirations
1.2	job and career/realizations
1.3	job and career/evaluations
(.....)	
5	**Income**
5.1	income/aspirations
5.2	income/realizations
5.3	Income/evaluations
(.....)	
8	**Children**
8.1	children/aspirations
8.2	children/realizations
8.3	children/evaluations

Methodology utilized to construct a meaningful pattern of facts involves;

1. Comparison of different text passages to find commonalities or differences between them.
2. Retrieval of all text segments belonging to the same code.
3. Analysis of text segments to find those elements which serve as criteria for comparison.

Advantages of CAQDAS have been highlighted by Lacey and Luff (2001, p.29). The main advantage for case study analysis is that data can be entered into the package as raw data which can be edited. Packages can search for words and phrases and provide frequency counts for content analysis and semiotics. The software also has

the advantage of being able to retrieve data contextually. Compared to manual coding, computer software coding is much simpler and less time consuming. Nodes or coded items can be stored and searched for across a wide selection of documents. Nodes can be combined with other nodes to construct conceptual models to develop theory.

The Ethnograph CAQDAS package is to be used for case study data analysis because it is compatible with Windows operating system and after an initial assessment of the current most popular CAQDAS packages the Ethnograph was found to be easily understood and only required a minimal amount of training. This software was one of the first programs to pioneer computer assisted qualitative data analysis. It permits analysis of typical case study data in the form of interview transcripts, case study notes and other text documents and has been utilized by social scientists, health researchers, business analysts and other qualitative researchers.

The application of CAQDAS to construction research is generally uncommon. However, Ball & Fortune (2000) have used Nud*ist successfully in their study of the development of environmentally friendly housing schemes. Data from key personnel interviews was analyzed to establish appropriateness of model selection categories and to uncover emergent sub-categories.
The use of such a software package in this study, for studying the validation of pharmaceutical facilities, provides an opportunity to further measure the appropriateness of this approach in data handling and analysis.

It has already been identified that the study will collect and analyse qualitative information. One such method that is applicable to case study fieldwork is that of participant *observation*. This methodology and application to the study is discussed below.

5.8 Participant Observation

According to Jorgensen (1989, p.12) use of participant observation is particularly applicable to research problems where little is known about the problem being studied. There may be different views between insiders and outsiders, and the phenomenon is somehow obscured from the views of the project outsider.

Therefore, studies of social situations require a unique methodology that allows the observer to be placed in the everyday setting of the observed.

5.8.1 Reality of the Insider

People give meanings to the world that surrounds them and they function on the basis of these meanings (Denzin, 1978, p.7). If people define their situation as real it is real in its consequences. The meaning of a situation or event may be misinterpreted or mistaken. This social group conception of reality is not directly accessible to nonmembers or outsiders who would experience this reality as a stranger (Schutz, 1967, p.144) and would be classified as undeveloped. It is suggested by Hall (1966) that for the outsider to achieve the greatest level of comprehension of the insider's world requires an understanding of the culture and language that is used to express its meanings.

Participant observation focuses on the insiders view of daily existence and uncovers the meanings people use to make sense of their daily lives (Spradley, 1980).

Bruyn (1966, p.27), whom defends participant observation, argues that the use of externally conceived 'scientific' measurement instruments, such as surveys, do not provide the best results as the two views of the reality being measured differ between the questionnaire writer and respondent.

5.8.2 Approaches to Participant observation

Participant Observation (2005) distinguishes between two approaches to this type of observation.

The phenomenological approach to participant observation, outlined by Bruyn (1966) has four main elements: awareness of time, physical environment, contrasting experiences and social openings and barriers. Generally speaking the participant observer strives to uncover the meaning of the experiences of the group from the perspective of those within the group.

Secondly, Zelditch, (1962, p.7) describes the analytical approach as consisting of three main elements: enumeration of frequencies, informant interviewing and participation. Here there is an emphasis on participation and systematic in-depth study.

There is no great distinction between the two approaches only a shift of focus between empathy and systematic observation and recording.

5.9 Observation strategy

5.9.1 Selecting and Entering the Setting

The selection and definition of the study problem will shape the observation setting. The appropriateness of the setting in relation to the problem will have an impact on the collection of information. Jorgenson, (1987) acknowledges the importance of the correct selection of the setting and the way that the setting can hinder or assist the observation. The more information that is known about a setting will help determine if the setting is in fact going to be appropriate in the context of the study. The lack of knowledge of the study setting could therefore greatly effect the quality and quantity of the observations made. Appropriate settings can also be selected on availability and convenience of access.

The *appropriateness* of the study is dependant on the participant observers ability to execute the participant roles in day to day situations. Therefore it is essential to have almost daily access to the project participants. Arguably, the most useful skill that should be possessed by the participant observer is the ability to successfully interact and gain acceptance within the insider group over a sustained period of time.

5.9.2 Access Strategies

Jorgensen, (1989, p.46) identifies two main strategies for gaining access to human settings. The *known observer* strategy involves the researcher making an application to observe, whilst the *unknown observer* method involves the researcher collecting information without the knowledge of those in the setting. This method is recognised by Punch, (2000, p.59) who argues that the researcher should consider issues of privacy, informed consent, ownership of data, and use and misuse of results.

The selection of a direct known observer strategy is a decision that is influenced by having knowledge of the politics of the setting and an ability to decide if the setting will prove successful. The use of unknown observer strategies have been described as ethically controversial and potentially harmful by Bulmer, (1982, p. 250). Defendants of unknown observation (see Riecken 1969, p. 43) argue that it would not be possible to carry out some studies, such as research of criminal behavior or drug use with the knowledge of those being studied.

If a complete known observation stance was taken everyone that came into contact with the participant observer would have to be notified of the research intentions. This would be impractical and inevitably result in some unintended deception. Other mixed mode approaches combining known and unknown observation strategies have also been used. Situations occur where access is gained without the knowledge of those being observed and later in the study the research intentions are disclosed to a small number of trusted participants (Fine, 1987). It could be argued that this disclosure might result in the cancellation of access if the participants were unhappy with the circumstances. On the other hand, this disclosure could prove advantageous and result in more pertinent information being made available via the informed insiders.

Jorgensen (1989, p.49) recommends that access to *backstage* regions of visible and public phenomena, such as corporations and factories, may be achieved by taking employment in the setting to allow unknown observation. Within the context of this study an opportunity existed for the writer to act as a validation engineer, providing construction quality assurance advice. It was from this view-point that observations were made.

Success of unknown observer strategies relies on the availability of appropriate roles and the extent to which the participant observer is able or willing to *learn* the functions of the role.

As discussed, there are a number of different approaches to entering the research setting. The success of each will depend on the creativity of the individual in response to the individual and unique setting. McCall & Simmons (1969, p.29) note that personnel attributes like experience, technical skills, age and sex, together with interpersonal skills and commonsense decision making are some of the main facets for gaining and sustaining successful entry. The outsider should therefore be familiar with the culture and language of the situation that is to be studied.

Jorgensen (1989, p.68) suggests that as we are observing everyday life we should try to minimize the extent of disruption in the field of study. Those being observed may behave differently if they are aware of the presence of an outsider or non-member.

The Hawthorn Effect, a phenomenon described by Roethlisberger & Dickson (1939) suggests that the way in which people work is influenced by the presence of a known observer.

It can therefore be argued that to effectively study a social situation the non-member must attempt to be as unobtrusive as possible so not to influence the actions of those around.

5.9.3 Social & Ethical Issues

The argument in favour of unknown or complete observer strategies is examined by Jorgensen (1989, p.48) who argues that those observed who interact with the researcher are unlike subjects of a survey or experiment. Observation occurs in the natural everyday surroundings of those being observed and is no different to the interaction of any other participant involved. The participant observer's focus is not unlike any number of special interests people have in interacting with each other.

Jorgensen (1989, p.28) argues that the participant observer has;

> no more of an ethical obligation to the people encountered in research than he or she would have under other everyday life situations and the researcher is therefore not obligated to inform people of the research intentions.

In participant observation studies in social situations such as those undertaken by Taylor (1987) the unknown observer strategy is arguably the most effective way of obtaining un-biased research information. The point is made by Jorgensen (1989, p.48), in studies into areas such as crime and deviance, that the level of success would be low if the observers were to declare their presence and purposes. Jorgensen (1989, p.29) also notes that; 'there is no way of absolutely ensuring ethical research'.

The focus of participant observation is that of the natural setting in which the participants are involved. While people provide and generate information they are not manipulated or maneuvered. A key ethical factor for the researcher to uphold in the field is to respect the anonymity and dignity of the observed. Acknowledging

this, all case study documentation has been edited to remove any reference to organizations or individuals.

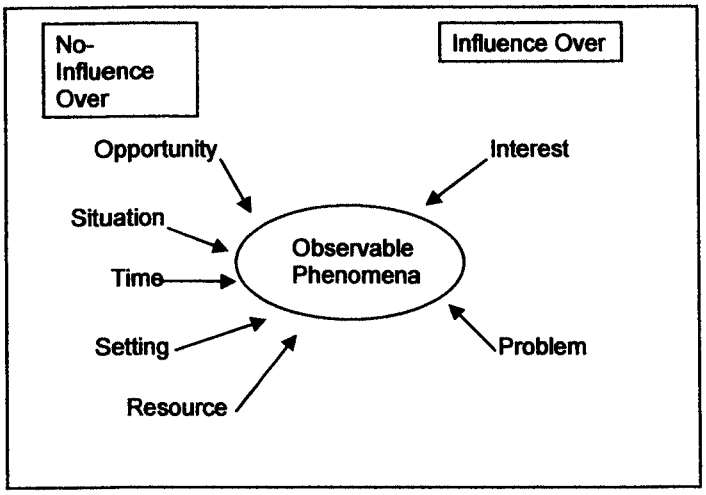
5.9.4 Making Observations

The initial problem in a study of this type is deciding on 'what' phenomena to observe and 'how' to observe it. Acknowledging Jorgensen (1989, p.50) that 'it is never possible to observe every possible setting or every situation that is of interest within a setting', a decision based on criteria such as opportunity, convenience and point of observation within organisation, has to be made. According to Dooley (1990, p.141) the two most common approaches to *sampling* are *probability* and *non-probability sampling*. The distinction between the two approaches is that the implementation of probability sampling involves the use of statistical formula to estimate the probability of error within a certain sample size. Non-probability sampling, or as often referred to, as *theoretical* or *judgmental sampling* in the context of participant observation is based on the observer defining a selection logic based on the nature of the phenomena. Selection logic is therefore dependant on the study problem and appropriateness of the setting for observation.

The sampling strategy known as *snowball sampling* is used to help generate phenomena for study based on an initial instance of the phenomena of interest. This initial phenomena of interest or study problem observation, is then used to generate additional cases for observation.

Figure 5.5 shows those factors that influence the strategy of non-probability selection logic used in theoretical sampling.

Figure 5.5: Observable Phenomena



Contributors to this area have successfully used different methodological approaches, for example Wallis (1977) used documents, questionnaire, interviews and brief observation. Fine (1987) concentrated on participation, observation and questionnaire and Hayano (1982) used observation and memory, making notes afterwards.

The approach depends on the field situation and literature indicates that there is no single set pattern of data collection.

Jorgensen (1989, p.82) distinguishes between two types of observation *focused* and *unfocused.* Unfocused observation of the physical landscape allows, at the outset of the field work, the observer to gain a feel for the social setting and to establish study focus.

Similarly Bresnen (1988, p.44) argues the need to establish, early on, a feel for the landscape.

5.10 Case Study Data Collection

Yin (1994, p.80) suggests that there are six primary sources of data that can be used as evidence in a case study. They are:-

1. Documentation.

2. Interviews.

3. Archival records.

4. Participant observation data.

5. Physical artifacts.

6. Direct observation.

The importance of multiple sources of evidence in relation to reliability is examined by Yin (1994, p.90). The case should generally use as many sources of evidence that are relevant as a means of increasing reliability. Sources of evidence have strengths and weaknesses in case study application; they are tabulated by Tellis (1997):

Table 5.6: Strength and Weaknesses of Case Study Evidence (Tellis 1997)

Evidence Source	Strengths	Weaknesses
Documentation	Stable – repeated view. Unobtrusive – exist prior to case study. Exact – names etc. Broad coverage - extend time span	Retrievability – difficult. Biased selectivity Reporting bias – reflects author bias. Access – may be blocked.
Interviews	Targeted – focuses on case study topic. Insightful – provides perceived causal inferences.	Bias due to poor questions. Response bias. Incomplete recollection. Reflexivity – interviewee expresses what the interviewer wants to hear.
Direct Observation	Reality – covers events in real time. Contextual – covers event context.	Time – consuming. Selectivity – might miss facts. Reflexivity – observers presence might cause change. Cost – observers need time.
Archival Records	As documentation. Precise and quantitative.	As documentation. Privacy might inhibit access.
Participant Observation	As direct observation. Insightful information into interpersonal behavior.	As direct observation. Bias due to investigators actions.
Physical Artifacts	Insightful into cultural features. Insightful into technical operations.	Selectivity. Availability.

5.11 Analysis of Case Study Evidence

The next stage of the case study, following the identification and collection of data, is to analyze the information that has been gathered. There are a great number of data

analysis methods available to the researcher. The most popular methods are summarized in table 5.7.

Table 5.7: Qualitative Research Data Analysis Methods

Analysis Method	Characteristics
Logic Analysis/ Matrix Analysis	An outline of generalized causation, logic reasoning.
Discourse Analysis	Linguistic analysis of group discussions.
Content Analysis	Emergent themes through text or speech documentation
Semiotics	Analysis of signs and symbols
Typology	Classification system of themes or patterns.
Grounded Theory/Constant Analysis	Inductive, theory discovery methodology
Taxonomy	Typology utilizing multiple concept levels.
Analytical Induction	Hypothesis generation based on a hypothetical view. Comparison of hypothesis with another event to compare. Hypothesis revision.
Narrative Analysis	Individual focus, similar to discourse analysis.
Quasi-statistics	Field note frequency of events and categories.
Event Analysis/Microanalysis	Analysis of boundaries and event beginnings and endings.
Metaphorical Analysis	Analysis of metaphors and observed fit. Validity of metaphor with participants.
Domain Analysis	Language analysis in a cultural context.
Hermeneutical Analysis	Analysis of written text. Not objective meaning, context meaning of cultural situations.

The data is analyzed by breaking it into segments that are of a controllable size, that allow the identification of patterns, sequences, classes, types or *processes.* The analysis process then consists of assembling the data in such a way that permits comprehension or meaning to be derived from the data.

By piecing together the research findings in this way and making sense of them, the process of theory building or theorizing can be said to be taking place. Jorgensen (1989, p.107) describes theorizing as an arrangement of facts in the form of an explanation or interpretation.

Within participant observation there are a variety of theorizing concepts which have been used successfully. *Analytic induction* (Bruyn, 1966) attempts to generalize from data by *abstraction.* Znaniecki (1965) discusses four steps to this practice: (1) determine the essential characteristics of a given class of facts; (2) abstract these features, assuming hypothetically that the more basic are more general than the less essential, and are found in a larger variety of forms; (3) test this contention by researching classes containing both the former and the latter class characteristics; (4) organize these classes into a system based on the functions of the characteristic in determining the particular form.

5.12 Validity and Reliability

A theory can be defined as a set of concepts and generalizations (Jorgensen, 1989). Participant observation methodology generates interpretative theories which provide an understanding of the phenomenon studied. The methodological aim is to build theories grounded in concrete human realities (Glazer and Strauss, 1967). To achieve this the process has to be flexible and open ended. Once the study problem is defined the researcher is able then to review and redefine the problem based on data collected in the field. Unlike positivist methodologies that employ experiments and surveys, studies using participant observation have gathered information concerning sets of 'broad themes' rather than hypotheses (Wallis, 1977).

Bresnen (1988) , who has utilized observation as a way of studying construction project organizations, acknowledges the need to evolve research methodology to suite the situation and goes on to acknowledge the reduced need for rigid structured methods of data collection in his own work.
Bresnen (1988, p.36) also points out that the small number of case studies in his research were valid in the context of his study, as he was able to use analytic generalizations whilst using a longitudinal component to fuse the studies key issues such as change and response.

The argument for the use of analytical generalizations over statistical generalizations is comprehensively discussed by Yin (1994, p.36).
It is acknowledged that the use of case studies as empirical research vehicles have been viewed as less attractive than experiments or surveys. Case studies can be seen to lack rigor and bias to influence the outcomes. A common concern is the use of statistical generalization when analysing a single or a small number of case studies.

Case studies like experimental research are generalizable to theoretical propositions and not to populations. The case study does not represent a sample and does not normally attempt to calculate frequencies.

Two types of generalizations can be made in research. The most common generalization methodology is statistical generalization, where inferences are made about a population based on collected empirical data about a sample. This

generalization method is often used because researchers have available to them methods for determining the confidence with which the generalizations can be made. These generalizations depend on internal variations and size within the population and sample.
Yin (1994, p.31), stresses that a common error made in carrying out case studies is to consider statistical generalization as the way of generalizing the case study results. Case studies are not sampling units and this generalization method is therefore inappropriate.

Analytic generalization uses a previously developed theory as a template or protocol with which to compare the empirical survey results. Yin (1994, p.31) states that 'if two or more cases are shown to support the same theory then replication may be claimed'. Analytic generalization can be used for single or multiple case studies and the aim with this method of generalization is to avoid thinking in statistical terms such as samples and consider a single case study as a single respondent in a survey or subject in an experiment. Level one inferences are commonly associated with statistical generalization but level two inferences, which deal with policy implications and theory are the goal.

The positivist approach to research is based on ensuring that the concept or phenomenon being observed is typical or common in everyday situations. This normally involves the utilization of statistical methods to achieve a valid presentation of the concept. Participant observations main concern is the definition of concept in everyday life and meaning. The result, according to (Jorgensen, 1989), is the generation of highly valid concepts.

Alder & Alder (1994) define the concept of validity in terms of the ability of the observer to penetrate the insiders 'world of action and meaning'. Limited access will generally result in less valid and reliable conclusions.

Unlike statistical generalization there are few set recipes for dealing with data at the analytic stage. There is great dependency on the researcher's individual style of rigorous thinking, presentation of evidence and consideration of alternative

interpretations. To assist this process analytic strategy is required. The analytic strategy goal is as follows:

1. Treat the evidence (data) fairly.
2. Generate analytic conclusions.
3. Rule out alternative interpretations.

Participant observation is commonly utilized as a method of qualitative enquiry used in case studies. Case studies can be used to research phenomenon related to culture, society, community, subculture, organization, beliefs, practices or interactions (Jorgensen 1989).

The objective of is to describe, comprehensively and completely, the events and incidents in terms of the research problem. In qualitative research it is not especially important if the case is part of or representative of a larger population, the quality and depth of information is however considered important. Case studies can be of the single or multiple type (Yin, 1994). There is an argument (Glazer and Strauss, 1967; Jorgensen, 1989; Yin 2003) that single case studies can be used for theoretical sampling. Theoretical sampling is a technique which does not rely upon the use of probabilities to select subjects.

Studies carried out (e.g. Ellis, 1986) involving two cases can enable the researcher to compare and contrast between the cases. Case study logic differs greatly to survey and experimental work which depends on the collection of data from a large population or demonstrating causal relationships by control and comparison of variables in the data sets.

A common theme in a qualitative study is that generally all of the data will be textual and will be either written or verbal. Many methods of textual analysis have been successfully used in qualitative research, such as discourse, content, conversation and hermeneutical analysis.

Semiotics (Denzin & Lincoln, 1994, p.358) can be used as an analysis procedure for textual qualitative data and will be utilized within the grounded theory-like structure of the analysis. Semiotics is concerned with assigning words to primary conceptual categories, where these categories represent important facets of the theory that is to

be tested. The relative significance of a category is revealed by the frequency in that it appears in the textual data. This supplementary analysis method will be used to gauge the importance of individual case study categorizations and generate and compare theoretical propositions across cases.

5.13 Analytic Analysis

It is recognized by commentators of qualitative techniques such as Yin (1994) and Tellis (1997) that there are various views on the analysis of qualitative data. One view is that *statistical robustness* is not an absolute necessity in all case studies.

The analysis step of case study research is considered by Yin (1994, p.102) as one of the areas of the process that is under developed and difficult. An Analytic approach suggested by Miles & Huberman (1984, p.239) involves using data arrays to show data, by matrix categorization, creating displays, tabulating event frequency, ordering information and examination of relationships. Bias must not be allowed to affects the process of generating and preparing the case study results. The researcher's interpretation and presentation of the results is shaped by previous experience of the problem phenomena and the available literature, Tellis (1997).
As mentioned previously, the use of statistics is not always required as some case studies do not allow analysis by statistical methods and the adoption of statistical techniques could affect other areas of the study.

The use of an analytic strategy is recommended for case study research as it first, helps direct the focus on what will be analyzed and second, establishes the logic for doing so. The main recommended methods of analytic analysis are pattern-matching (Trochim, 1989), explanation building (Yin, 1994) and time-series analysis (Kidder, 1981).
The case study analysis of this thesis is based on a combination of the general analytic methods of theoretical propositions and a grounded theory-like approach to pattern matching. The study relies on generation of a number of hypothetical questions or propositions which are presented in chapter four, and also the comparison of a predefined pattern that is represented in the third order validation cybernetic model. An element of time series analysis is also used to examine the

sequence of validation activities in relation to the model. By comparison of the sequence of the validation activities of DQ, IQ and OQ, to a pre-specified sequence (defined in the model), replication and structural correspondence can be assessed and explained.

5.14 Study Data Categories

The use of logical categories for data analysis have been utilized by writers such as King & Kraemer (1985) and Tellis (1997). Categories including technological development, structural arrangements, socio-technical interface, political economic environment and benefits and problems have been developed and used in case study analysis.

By adopting similar category logic and modifying the categories, to suite the objectives of this study, the following categories were developed from the literature review, for analysis. Those categories are:

1. Culture and Attitude (project environment)
2. Planning ((time and cost), communication, integration, resource).
3. Implementation (control and sequence, change and partnering).
4. System Complexity (termination, start-up and commissioning)
5. Quality and Regulatory Compliance

The data categories are all linked by, what King & Kraemer, (1985) term, *functional equivalence,* which means that the same variable may be measured by a variety of different indicating factors, all of which have some influence on the phenomena. This concept has been highlighted in previous chapters, where it was noted that themes or categories appear to be related by the three key emergent themes of regulatory understanding, experience and, as previously discussed in chapter 2, attitude and culture.

The data categories or parent codes, one to five, are divided into a larger number of child codes to allow coding of the qualitative data sources.

Once the case study data had been collected the data are entered into a *data matrix.* The matrices represent data from interviews and a wide range of case study qualitative data sources including an industry survey.

5.15 Study Data

Three case studies are undertaken, each generating a set of qualitative data with multiple sources of evidence being collected during each field study period. Following the field-work study, the primary data is supplemented by undertaking an industry based survey. The survey, in the form of a questionnaire was sent to seventy five organizations which included construction and pharmaceutical companies. The survey responses generate two distinct data sets; construction and pharmaceutical.

Manual analysis techniques, such as manual data coding and sorting, are aided by the use of two computer software packages, the Ethnograph and (SPSS) Statistical Package for Social Sciences.

5.16 Study Level of Analysis

Although most research is carried out under the umbrella of either quantitative or qualitative work, researchers have suggested combining one or more research methodologies in one study to aid in *triangulation.* Accounts of triangulation can be found in Mingers (1995) and Ragin (1987).

As previously noted analytic strategy in research does not normally employ the use of statistical analysis. However, for the reason above, statistical software packages, such as SPSS are able to permit statistical analysis of qualitative data.
Statistics are defined by Williams (2003, p.127) as a 'collection and interpretation of numerical data'.
There are three levels of measurement that are important in social research, *nominal, ordinal* and *interval.* Nominal measurements have the least meaning and lowest *power,* such as a persons name. Ordinal variables are more informative and are therefore more powerful. These variables give the order or rank of the data but will not give *distance* information between the measurements. The most powerful measurement is the interval variable, here; the same scale difference has the same meaning.

The data gathered from the research is of the nominal and ordinal measurement types and therefore the choice of descriptive statistics, frequency tables and output displays is dependant on the level of measurement of the variables.

Univariate or descriptive statistics form the basis of the study statistical analysis. In fact as Williams (2003, p.128) comments, univariate statistics represent the most commonly presented type of analysis.
Univariate or single variable analysis gives the counts or frequencies for the values within a variable. This is a form of descriptive statistic of the type computed in SPSS. Such analysis has the advantage of being able to *compare* sets of data through the use of tables, charts and graphs. *Cross-tabulations* analysis permits the discovery of the relationship between two variables. This is often presented with statistical analysis to show if the sample has certain characteristics which allows decisions to be made on the validity of our generalizations. These tests are based on probability and are central to statistical analysis techniques.
Cross-tabulation or *contingency tables* allow *bivariate* analysis of data sources, the aim being, to show a statistical relationship between the variables. In addition several variables can be examined by a more complex process of multivariate analysis. These *associations* are a measure of the strength of significance and cannot show us causal relationships.

5.17 Summary

The initial stages of the study proposed a set of relationships between dependant and independent variables. These initial theoretical propositions provide a framework of study, which was initially based on experience and literature. Now, with the selection of appropriate research techniques, highlighted in this chapter, the study has addressed the three research aspects or paths suggested by Brinberg & McGrath (1985), that are central to their *Validity Network Schema* (VNS) concept, and are termed substantive, conceptual and methodological domains.
VNS represents the relationship of different aspects of validity at varying stages within the research. Brinberg & McGrath (1985, p.15) describe that research has different paths, levels and stages and acknowledge all paths are flawed in what can

be achieved, they go on to argue that to successfully research a phenomena requires the pursuit of multiple paths. This study adopts such an approach by combining experimental and empirical paths to provide interpretation through observation, which is achieved by building structure through study design and implementation.

Having selected an applicable research methodology and suitable research tools, the cybernetic validation model can be analyzed within the context of the analytic phase of the study. Chapters Six, Seven and Eight present the data collection and analysis from three case studies, Cases A, B and C.

The results of the first of the case studies, Case A, are used to build upon those problematic themes[1] previously established to develop code categories. These produce a multi-code family tree which can be used to compare emergent category themes and data set overlap from case studies B and C and a questionnaire survey presented in Chapter Nine.

Case A is also used to analyse the implementation of the validation process over time through pattern matching to test for replication and structural correspondence

The results and analysis of the case studies and survey are presented in Chapters Six, Seven, Eight and Nine.

[1] See Chapter 3, Figure 3.8.

Chapter Six: Case Study A – Results and Analysis

This chapter presents the first of three case studies and is in-line with the case study methodology outlined in chapter five. The chapter displays and analyses qualitative case study evidence from case study A.
The aim of the study is to build upon the problematic theoretical themes from Chapters Two and Three, and to:

1) Develop code categorizations and produce a multi-category code family.
2) Utilize the multi-category code family tree data sets on case studies B and C.
3) Use data matrices to compare emergent category themes and data set overlap (from data sets A, B and C).
4). Analyse the implementation of the validation process model over time and use pattern matching to test for replication and structural correspondence.

6.1 Case Study Projects

Figure 6.1 shows the three case study projects.

Figure 6.1: Summary of Case Study Projects

Case Study Identifier	Facility Type	Scope of Validation Activity	Date
A	Low volume tablet production suite (Tablet compression, coating and packaging).	HVAC services, GMP Enclosures.	2000 - 2001
B	Dispensary (Liquid and solids).	HVAC services, GMP Enclosures, Purified water system.	2001 - 2002
C	Oral solid dose tablet compression suites (Phase 1 and 2).	HVAC services, GMP Enclosures.	2002 - 2003

All data was obtained through observable situations over a field-work period of four years. Data sets A, B and C are included in appendix B and contain observation data in the form of memos, letters, protocols, schedules, presentations, meetings, interviews, reports and audit information. Manual coding of observation data is referred to, for example, as A4, C25, in the discussion of the case studies and is used as a way of providing evidence in support of the discussion. Here the letter A, B or C

refer to the case study identifier and the number refers to the code book family tree code (see figure 6.7).

Computer assisted coding using the Ethnograph software package is presented in the following format:

(Case study group – Code (or sub-code) - Line where code occurs in the text)

e.g. (Cl1- COMPCON-297)
Cl1 – Client 1
COMPCON – Complex Construction
297 – Line 297 in the coded text.
or
e.g. (VSP1-QUALUN-100)
VSP1 – Validation Service Provider 1.
QUALUN – Quality unaware.
100 – Line 100 in the coded text.

Figure 6.2 outlines the project team members associated with each of the case studies and the types of qualitative data that was accessible during the fieldwork period.

Figure 6.2: Case Study Groups and Qualitative Data collection Methods

Case Study Identifier	Client (Cl)	Contractor (C)	Validation Service Provider (VSP)	Qualitative Data Collection Methods
A	Client 1 (Cl1)	Contractor 1 (C1)	Validation Service Provider 1 (VSP1)	- Interviews - Diary Notes - Memos - Observation - Validation protocols
B	Client 1 (Cl1)	Contractor 2 (C2)	Validation Service Provider 2 (VSP2)	- Schedules - Informal Interviews - Observation - Memos - Validation protocols. - Audit reports.
C	Client 1 (Cl1)	Contractor 2 (C2)	Validation Service Provider 2 & Client 1. (VSP2) (Cl1)	- Schedules - Informal interviews - Observation - Programmes - Minutes - Memos - Validation protocols

6.2 Main Area of Data Collection – Case Studies

6.2.1 Case Study A

This chapter presents case study evidence from the fieldwork study and the initial sensitising interviews with the design and build contractor (C1) and the client validation manager (Cl1). Code categorizations are presented in the form of a three level code family tree, indicating parent and child levels. The theme classifications were then used to code and theoretically sample the qualitative data of the subsequent studies (B and C). Participant observation of case study A was

undertaken prior to the sensitising interviews and the data from the observation study was re-coded in line with the outcomes of the initial orientation research.

6.2.2 Project Details

The project location was a pharmaceutical manufacturing centre in the north east of England. The facility was owned by a large international pharmaceutical company who had plants in Italy, Spain, France and Brazil, and who specialised in organic chemicals/intermediates, plant and animal products and customer contract manufacturing.

A number of key drivers were identified as reasons for site re-development, they were:-

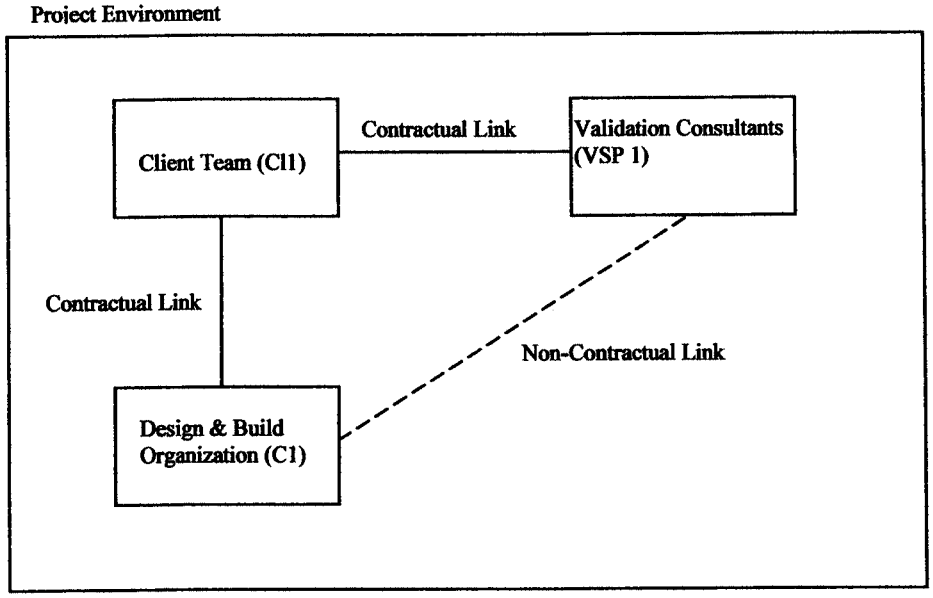
- The impact of a large reduction in production products for a contract manufacturing client and the need to redevelop parts of the facility for new business.
- Increase product portfolio/capacity requirements.
- Ensure facility quality requirements.
- The need to refurbish existing parts of the facility.
- Efficiency opportunities i.e. ability to reduce costs by more efficient facility construction/services and processes.
- The need to comply with American regulatory standards (FDA) to realise new market opportunities.

Having identified the need for site re-development the client considered various options, including moving to a new 'green field' site. Following a financial analysis of all possible options a decision was made to re-develop the existing manufacturing facility by the process of demolition and re-build.

As part of the sixty million pound site upgrade, a number of new facilities were built, the first of these, the focus of case study A and possibly the most important, was the construction of a pharmaceutical pilot plant comprising of a tablet compression suite, tablet coating suite and packaging hall.

The construction of a pilot facility was within a large existing warehouse at one end of the site. The facility was designed and constructed for the client (Cl1) as a fully functional production facility as a way of setting benchmark standards for future sites within the manufacturing organization. The project had an initial construction programme duration of seven months (February 2000 to August 2000). The design and build project was structured as follows:-

Figure 6.3: Case Study A Project Environment



The main groups involved in the project were the client (Cl1), design and build contractor (C1) and the Validation service Provider (VSP1). The clients organizational consisted of quality assurance, production, packaging, logistics, engineering, health and safety, purchasing and finance departments. The main contracting organization was a national design and build company, with its head office based in the north of England. The contractors business was split into sectors which consisted of mechanical and electrical building services contracting, clean room construction and general construction. Validation services were provided by

the UK representative of a large multinational consultancy. The organization was located in the south east of England.

6.3. Sensitising Interviews

Interviews were undertaken to: 1) assess the data collection method as an instrument for use in the main case studies; 2) clarify, corroborate and focus attention on the specific developing study propositions and categorizations – operationalisation; 3) provide, by grounded theory methodology, a multi-level code family tree to use in subsequent case studies.

The first interview was carried out with the construction project manager of contracting organization, Contractor 1 (C1) and the second interview was undertaken with the validation manager of the pharmaceutical manufacturing organisation, Client 1 (Cl1).

Both interviews were carried out at Cl1's manufacturing facility. The selection of the interviewee was based on his proximity to the problem setting and the informant's role within the project environment. During the early stages of the project the two most suitable team members, who represented both the client and main contracting organization, were identified. Based partly on the development of an increasingly good rapore with the interviewees, it was suggested that they may be interested in taking part in an interview. This development and maintenance of a good field relationship is discussed by writers such as Jorgensen (1989), who note that the collection of accurate and defendable information can be compromised by unfriendly and untrustworthy relationships.
The semi-structured interview questions were based around a number of *groupings* based on a framework adopted by Stringer (1996, p.65) as shown in figure 6.4.

Figure 6.4: Basic Question Groupings (Stringer 1996)

Grouping	Description
Places:	Offices, location of activities and events; physical layouts.
People:	Individuals, types of people, formal positions and roles.
Objects:	Buildings, furniture, equipment and materials.
Acts	Single actions people take, group actions.
Activities	A set of related acts.
Events:	A set of related activities.
Purpose:	Purpose: what people are trying to accomplish.
Time	Times, frequency, duration and sequencing of events and activities.
Feelings	Emotional orientation and response to people, events, activities and so on.

Specific research questions, those that relate to the basic grouping areas, were generated together with the basic categorization scheme noted by Yin (1994, p.20), which include the "who", "what", "where", "how" and "why" questions.

Each interview was recorded and then transcribed as a computer electronic document. The document was then coded and analyzed by using the Computer Assisted Qualitative Data Analysis Software (CAQDAS) package the Ethnograph. The full coded interview texts and interview questions are included in appendix A and B.

6.4 Project Environment

Within large manufacturing organizations like C11, the socio-technical system is based on the process of manufacturing. Upon the introduction of the construction project comes a change in the structure of the organizational environment. This change results in increased demands on the client's resources (C11-IMPRES-288). Client manufacturing and support departments, such as engineering and maintenance, have to adapt to accommodate the new facility into their existing operational structure.

Communications problems exist within large projects that have a large number of multi-disciplinary teams. The client noted that there were communications problems, (C11-IMPCOM-297), that resulted from 'not speaking enough' and there being 'so many different groups' involved in the project. The opportunity to meet and discuss project progress and problems was summarised by the client;

> we didn't get together often enough and talk about proper problems...those meetings were just moaning on about costs. (C11-IMPMEET-305, C11-IMPER-309).

The client groups who had the largest role in managing the project were the engineering director and the user group manager (production) and they had therefore the greatest contact time with the construction team. Communications links and cross discipline understanding between the client's quality assurance function and the construction organization are factors suggested by Southerland, (2000) and Leach (1990) that have a major influence on the validation process. The client's validation manager noted that;

> in the building project there was probably a lot that went on that I didn't know about.

The validation manager did not have clear lines of communication with the construction group and this hindered progress, resulting in re-testing of systems and delay (C11-EXPIN-530). The contractor recognized that there were specific communications problems, and said on the subject of meetings;

> when they did happen there seemed to be too involved...there seemed to be a mass of people there and nothing ever seemed to be achieved..it was the guy who was running the project was from a construction background and maybe didn't fully understand the pharmaceutical industry..in fairness the expertise was there but I think it just got lost in such heavy meetings. (C1-IMPLEMENTA-472).

An initial study proposition that suggested the geographical location of the VSP's head office to the construction site may affect project performance was discussed

with the client, who refuted this and suggested that this was not a problem on this project. The client did however point out that performance appeared to suffer when consultants were employed on a number of different projects (C11-IMPCOM-460).

A comment made by the client's validation manager that is worthy of note relates to the use of systems and equipment vendor validation documentation. There is an attraction to use vender validation documentation to ease project resource. The content of this type of testing protocol should be met with caution (C11-591) as it is suggested that the vendor may not provide sufficiently well developed protocols that comply with current regulatory GMP legislation.

The interface between the pharmaceutical and construction biased project groups can result in a 'clash of cultures'. C1 indicated that the relationship between the VSP and C1 was 'pretty poor' and VSP 'tended to back off and leave everything to C1' (C1-IMPLEMENTA-351, C1-IMPLMODEL -358).

The importance of the contribution of an experienced commissioning specialist is often not recognised. The commissioning project group act at the interface between the clean technologies of the project environment and the construction environment and are central to achieving the client's requirements. Project operation and maintenance documentation packages are required by the validation service provider to allow assessment to be made of the operational conditions of the production environment. The completeness and clarity of presentation of this detailed technical information depends the detail of request by the client from the contractors commissioning organization. The benefits of using a commissioning specialist with previous experience of providing quality related data, that could be of use to the validation process, was evident from the interviews. The commission engineers input was described by contractor C1 as;

> invaluable..because he just pulled all of the commissioning together..including all the test packs for the validation or to assist with the validation.. with all the pressure regimes and the way the systems integrated I honestly don't think that a site engineer and a few commissioning guys, run-of-the-mill balancing technicians would have been able to do the job (C1-VALIDGEN-681).

6.5 Implementation – Control and Sequence

When questioned about the timing of the validation activity the interview responses confirmed that the process should have started earlier (C11-TDEARL-60) and the extent of involvement was unclear (C1-CONLOO-17, C1-QUALIN-22).

This late stage implementation was also cited by the contractor (C1-IMPLMODEL-288), who suggested that there was limited input by the client resulting in later problems.

The interview response given by the contractor confirmed that the commissioning stage of a project is considered as a buffer between construction and hand-over where;

> we envisaged that it would get a lot more involved around commissioning stage...that's what everything gets tagged onto really (C1-TDLATE-105, C1-COSTCOM-105, C1-TIMPCOM-110).

There was a User Requirement Specification (URS) produced for the site re-development works. However, the client's validation manager thought that the VSP did not fully understand the client's requirements (C11-EXPIN-540). One reason for this was that there were continual design changes throughout the project which were not captured, communicated and documented to provide effective change control. The main contractor indicated the VSP was experienced in the area of process validation (C1-EXPSO-250) but did not comment further on their other areas of expertise. This situation is relatively common for the VSP to be from a science background, this may be due to validation activity having its beginnings in the quality assurance process of pharmaceutical manufacture.

The validation process sequence is not always in line with that recommended in the literature (audit/regulator). The client stated that Good Manufacturing practice (GMP) reviews of the design were carried out by the design team and that the local representative of the MCA (now MHRA) attended site to look at the design (C11-TDEARL-76, CL1-IMPLEMENTA-76). The client's validation project manager did not attend any of the design review audits or meet with the regulatory inspector.

When discussing this subject, the validation manager referred to the project group as 'they' indicating a detachment from some of the critical process steps.

Variations in design have a direct affect on the validation (C11-COST-146), C11-TIMPLAN-138) costs and schedule. Design changes were often not reflected in the validation testing protocols due to poor communications within the project team.

Calculation of the duration and cost of the validation works is commonly based on the experience of the project manager (C11-TIMPE-233, C11-COSTPEX-253). The accuracy of this technique can be affected by the availability of certain project team members and equipment suppliers. The ability of the validation and commissioning teams to sequence common testing procedures that form part of the commissioning and validation activities are affected by communications problems and unclear contractual frameworks (C11-TICOM-237).
Increasingly contractors are forming a partnering alliance with sub-contractors in an attempt to foster an environment of reduced risk and mutual benefit. This was borne out in the interview with the contractor (C1-200) who suggested that having a commissioning manager involved in the project assisted the communications process between contractor and client. This process is referred to by James (1998) as *streamlining* and seeks to increase integration to reduce project validation time and cost.

The correct sequencing of the validation activity is required to be in line with the recommendations of ISPE (2001) to achieve the maximum benefits from the process. Contractor C1 noted that;

> validation..it flags things up and if done at the right time can flag up potential problems (C1-VALIGEN-525, C1-VALIQ-526)...its quite simple to go out there and do run of the mill balancing (commissioning)..its very straight forward, but when you are talking about integrated process and mechanical services systems, with the way that the validation goes into more detail that problems are found at an earlier stage. (C1-VALIQ-541).

The system steering control benefits of carrying out installation qualification tests at or close to the installation stage were underlined by an example given by contractor C1;

> a prime example ..is the filter situation we had where we had ordered filters (high efficiency) that were specified..the wrong filters where delivered and subsequently installed without checking...the validation team checked them and they were found to be wrong so they had to be taken out..under normal circumstances that may not have happened or been even found out or would not have been important.

In this example the advantages of validation as an installation verification and corrective steering process were borne out. The outcome of this example relied on the identification of critical items of installation equipment and plant. The validation process identifies that the environmental conditions within the space are critical to the manufacturing process. As contractor C1 noted, under normal circumstances the discovery of inappropriate environmental conditions would have not been important within the 'normal' construction project. The understanding of the client's environment and interpretation of this into a working, compliant design are aided by the validation activity.

Effective communication is required to ensure that the validation and commissioning groups who will be closely involved schedule common tasks. Contractor C1 acknowledged this;

> if you don't make them (commissioning organization) aware that there is a validation team looking over their shoulder it can be a bit more long and drawn out..the upshot of it is, if its understood at every stage what's appreciated and what the validation team want then we can build that time in ..the problem is if they don't do that and it's not made aware to all early enough. It can be a problem.

6.6 System Complexity

In pharmaceutical construction projects complexity and the way that different groups view the project are very different. The complexity focus of the client is the integration of the manufacturing process systems and the building (Cl1-COMPLEXITY-27). The client's view of the building is that it is of a lesser importance than that of the process, to the extent that the structure housing the process is termed as an enclosure. The contractors focus is primarily that of the building and its associated services. The introduction and accommodation of complex process systems presents an element of risk (C1-COMPPRO-291,

COMPMONAL-291, COMPAUT-291) to the contractor. An example of this was described by the contractor;

> if the system or equipment is new and has not been sufficiently looked into or researched then it arrives on site and all of a sudden there are ten extra electrical supplies, water supplies, mechanical supplies that are needed ...is there a distribution board, that sort of thing that becomes a problem..also holes being cut in floors for equipment shoots, next thing you need to be trimming structural steel..it has a knock on effect, things aren't as simple..there are so many repercussions that have to be taken into account.

Large manufacturing equipment that is integrated into the building has a major impact on the validation of the environmental monitoring and HVAC systems. During the installation of a large integrated tablet coating system there were operational problems that required extensive remedial works. This re-work resulted in modifications to the equipment and additional utility connections which in turn compromised the HVAC system performance. Not until the equipment problems were rectified were the final validation OQ HVAC and monitoring tests completed (C11-EXPIN-530).

Changes in position and location of such complex manufacturing equipment may often mean that modifications to the design of the building and associated systems are also required. These modifications may have an impact on other sub-systems that have interfacing environments. In case study A Mechanical and electrical sub-systems were modified to allow re-positioning of process equipment. Contractor C1 noted that;

> ..I think we caught it early enough, nothing had been tested at that stage and it didn't result in a re-test of the ductwork system ..there were no significant changes to the air handling units or internal components (C1-646).

Although these changes were seen having no significant effect to contractor C1 they did result in changes to the validation testing protocols and plant record drawings.

6.7 Quality and Regulatory Compliance

The client's validation manager's interview revealed that there were concerns over the content and feasibility of execution of the validation consultants testing protocols (Cl1-EXPIN-321, Cl1-EXPIN-327).

The confusion in understanding the quality requirements of different regulatory authorities was borne out in an interview with the client. The difference between UK and USA regulatory expectations was vague (Cll-EXPSO-99, Cl1-IMPLEMENTA-98). There was an understanding that the MCA audits resulted in a verbal communications of the suitability of the design, but with no written report. This is in line with the literature, however, when questioned about FDA expectations, Cl1 made the point that the FDA would look at validation in 'a bit more detail' suggesting that the level of compliance would be more demanding.

Understanding the regulatory legislation regarding GMP in the pharmaceutical industry and implementing a successful validation strategy to achieve it, requires that the project group be sufficiently familiar with the quality environment. The client was aware of the GMP levels to be achieved but did not fully understand how to achieve them in a changing design and build construction environment (Cl1-548). At the time of the prototype project the client's quality assurance change control program was not yet in place.

The main contractor was unaware of the compliance levels to be achieved and viewed this as the validation services providers' responsibility (C1-IMPREQ-139). The contractors design responsibility was achieve those levels set out in the contract documentation. Those levels of design standards were, as C1 put it;

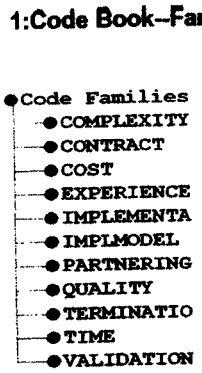
> the only sort of approvals we were working towards or standards where the actual clean room standard which we had to achieve..which was pretty unknown (C1-IMPREQ-139).

The project quality standards are normally set out in the URS and this is interpreted by the designer who confirms that the design meets the specified performance. This is normally included in the project functional specification (FS), by the design group. The early stage project documentation confirming the project specification and functional appraisal were not adequate for the project (C1-VALIDFS-148).

6.8 Code Categorization

Each of the interviews was transcribed and a Microsoft word processing file was imported into The Ethnograph software package. Project data files were created through the 'project manager' function of the program and the editor function was used to format the data to prepare it for family tree parent coding. The initial code themes that resulted from the sensitising interviews are shown in figure 6.5.

Figure 6.5: Code Categorization - Parent Code Level



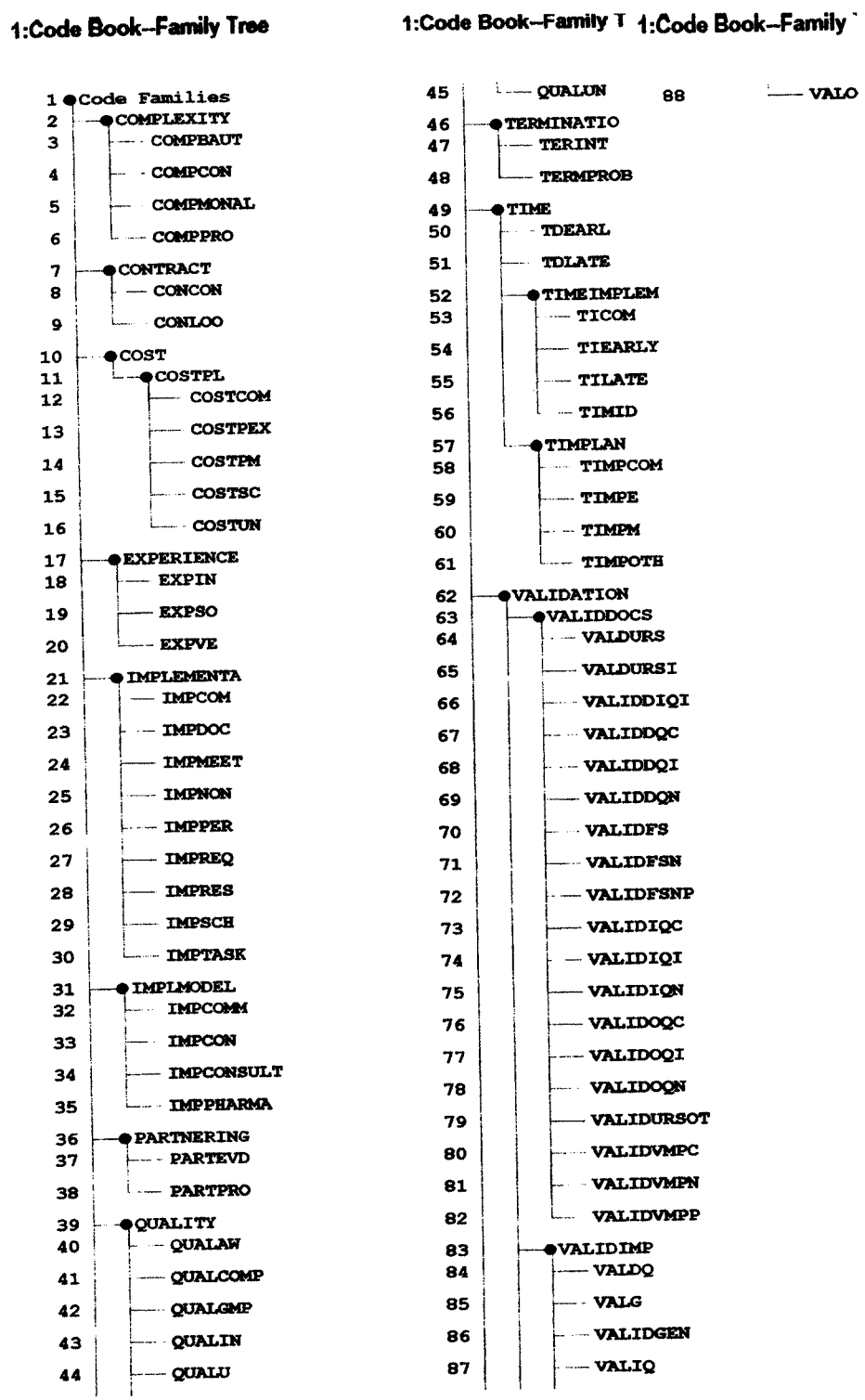
The *code procedures* function of the program was used to develop and define a code family tree. The first level of the code category family tree was based on the review of literature and subsequent generation of theoretical propositions. The second and third levels of sub-codes were added to the initial code themes. The full code family tree that emerged from the data is shown in figure 6.7. The coding procedure function of the Ethnograph was used to add *memos* to the coded interview data. The *memos* show theoretical propositions that were observed through the relationship between family tree codes. The process of theoretical sampling occurred until the examination of the codes and memos was completed and no new properties could be added. Figure 6.6 shows an example of the categories that emerged from the process.

Figure 6.6: Example of Code Book (See Appendix B for full code book)

1:Code Book--Summary

Code Word	Parent	Text	Definition	Modified	Added
COMPBAUT	COMPLEXITY		Complex building with automated	28/06/05	00/00/00
COMPCON	COMPLEXITY		Complex construction	28/06/05	00/00/00
COMPLEXITY	None		Project Complexity - complex	28/06/05	00/00/00
COMPMONAL	COMPLEXITY		Complex monitoring/alarm systems	28/06/05	00/00/00
COMPPRO	COMPLEXITY		Complex manufacturing process	28/06/05	00/00/00
CONCON	CONTRACT		Contract is based on quotation	28/06/05	00/00/00
CONLOO	CONTRACT		Loose contractual format	28/06/05	00/00/00
CONTRACT	None		Contractual arrangement of	28/06/05	00/00/00
COST	None			28/06/05	00/00/00
COSTCOM	COSTPL		Cost based on commissioning time	28/06/05	00/00/00
COSTPEX	COSTPL		Cost based on experience	28/06/05	00/00/00
COSTPL	COST		Validation cost planning	28/06/05	00/00/00
COSTPM	COSTPL		Based on planning matrix	28/06/05	00/00/00
COSTSC	COSTPL		COST BASED ON SUB-CONTRACT	28/06/05	29/06/05
COSTUN	COSTPL		Cost - unplanned	28/06/05	00/00/00
EXPERIENCE	None			28/06/05	00/00/00
EXPIN	EXPERIENCE		Inexperienced - of pharmacutical	28/06/05	00/00/00
EXPSO	EXPERIENCE		Some experience - of	28/06/05	00/00/00
EXPVE	EXPERIENCE		Very experienced - pharmaceutical	28/06/05	00/00/00
IMPCOM	IMPLEMENTA		General communications problems	28/06/05	00/00/00
IMPCOMM	IMPLMODEL		Commissiong group is VSP	28/06/05	00/00/00
IMPCON	IMPLMODEL		Main contractor is VSP	28/06/05	00/00/00
IMPCONSULT	IMPLMODEL		Consultant is VSP	28/06/05	00/00/00
IMPDOC	IMPLEMENTA		Specific test documentation	28/06/05	00/00/00
IMPLEMENTA	None		Implementation characteristics	28/06/05	00/00/00
IMPLMODEL	None		Validation service provider model	28/06/05	00/00/00
IMPMEET	IMPLEMENTA		Problems associated with	28/06/05	00/00/00
IMPNON	IMPLEMENTA		None attendance of task groups	28/06/05	00/00/00
IMPPER	IMPLEMENTA		Quality of implementation	28/06/05	00/00/00
IMPPHARMA	IMPLMODEL		Pharmaceutical organization is	28/06/05	00/00/00
IMPREQ	IMPLEMENTA		Difficulties understanding	28/06/05	00/00/00
IMPRES	IMPLEMENTA		Too few resources	28/06/05	00/00/00
IMPSCH	IMPLEMENTA		Implementation schedule problems	28/06/05	00/00/00
IMPTASK	IMPLEMENTA		Problems of task implementation	28/06/05	00/00/00
PARTEVD	PARTNERING		Evidence of partnering	28/06/05	00/00/00
PARTNERING	None		Partnering	28/06/05	00/00/00
PARTPRO	PARTNERING		Partnering issues	28/06/05	00/00/00
QUALAW	QUALITY		General apprciation of quality	28/06/05	00/00/00
QUALCOMP	QUALITY		Quality - aware of specific	28/06/05	00/00/00
QUALGMP	QUALITY		Quality-aware of specific GMP	28/06/05	00/00/00
QUALIN	QUALITY		General interest shown in quality	28/06/05	00/00/00
QUALITY	None			28/06/05	00/00/00
QUALU	QUALITY		Quality uninterested - limited	28/06/05	00/00/00
QUALUN	QUALITY		Quality Unaware	28/06/05	00/00/00
TDEARL	TIME		Time - Design Stage - validation	28/06/05	00/00/00
TDLATE	TIME		TIME - Design Stage- validation	28/06/05	00/00/00
TERINT	TERMINATIO		Integrated termination	28/06/05	00/00/00
TERMINATIO	None		Termination project phase	28/06/05	00/00/00
TERMPROB	TERMINATIO		Termination problem	28/06/05	00/00/00
TICOM	TIMEIMPLEM		validation at time of	28/06/05	00/00/00
TIEARLY	TIMEIMPLEM		Early implementation of	28/06/05	00/00/00
TILATE	TIMEIMPLEM		Late validation implementation	28/06/05	00/00/00
TIME	None		Time - schedule/prog.	28/06/05	00/00/00
TIMEIMPLEM	TIME		Time of implementation	28/06/05	00/00/00
TIMID	TIMEIMPLEM		Mid stage implementation of	28/06/05	00/00/00
TIMPCOM	TIMPLAN		Validation based on commissioning	28/06/05	00/00/00
TIMPE	TIMPLAN		Validation planned on experience	28/06/05	00/00/00
TIMPLAN	TIME		Planning of time/cost of	28/06/05	00/00/00
TIMPM	TIMPLAN		Planning matrix used	28/06/05	00/00/00

Figure 6.7: Three Level Code Category Family Tree



6.9 Semiotic analysis

To determine the frequency and importance of emergent themes a *multiple code frequency search* of the data files was conducted using the software package. An example of the summarized code frequency search is shown in figure 6.8.

Figure 6.8: Example of Summarized Code Semiotic Analysis

FREQUENCY PRINTOUT 05/07/2005 12:41:21 Page 2
(Top PCT is % across files. Bottom PCT is % within the file.)

CODE WORD	COUNT	PCT	CODE WORD	COUNT	PCT	CODE WORD	COUNT	PCT
File:CL1-VALI								
COMPLEXITY	1	1.00 0.03	COMPBAUT	0	0.00 0.00	COMPCON	0	0.00 0.00
COMPMONAL	0	0.00 0.00	COMPPRO	0	0.00 0.00	CONTRACT	1	1.00 0.03
CONCON	0	0.00 0.00	CONLOO	0	0.00 0.00	COST	1	1.00 0.03
COSTPL	0	0.00 0.00	COSTCOM	0	0.00 0.00	COSTPEX	1	1.00 0.03

Semiotic analysis was carried out across each of the interviews and the results are tabulated in figure 6.9.

Figure 6.9: Case Study A Interview Data – Semiotic Analysis (Contractor C1 and Client Cl1)

Code Group	Client 1 (Cl1) Code Frequency	Contractor 1 (C1) Code Frequency	Client (Cl1) Code Percentage	Contractor 1(C1) Code Percentage
Complexity	1	3	3.2	5.4
Contract	1	3	3.2	5.4
Cost	2	2	6.4	3.6
Experience	5	3	16	5.4
Implementation	8	15	25.6	27.27
Implementation Model	3	3	9.6	5.4
Partnering	0	2	0	3.6
Quality	0	7	0	12.72
Termination	2	0	6.4	0
Time	6	4	19.2	7.27
Validation	3	13	9.6	23.63

From the interviews a number of particular important issues and differences emerged which related to the study propositions. Observed commonalities between the two

interviewees were represented by high frequency counts in the *implementation* categories. The *implementation* theme contains sub-categories which consist of specific characteristics relating to problems associated with, *communications, project personnel, understanding, resource, schedule* and *tasks*. There appeared to be a general acknowledgement of problems of this type between the two informants.

Differences are exhibited by the occurrence of dissimilar frequency counts. The greatest differences occurred in the categories of *quality, validation* and *time*. Examining each in turn , the main contractor demonstrated that his organization were committed to providing a quality service, noting that, 'it is better to complete a project right first time than having to return to site to rectify shoddy workmanship'. Although the categorizations pointed to some general awareness and interest in pharmaceutical quality requirements (C1-64, 20, 417), in general, there was a demonstration of limited understanding of regulatory requirements related to the construction of the prototype building (C1-143, 405).
This can be demonstrated from the following code pattern:

QUALIN-QUALAW-QUALUN-QUALITY-QUALIN-QUAL-AW-QUALAW

From the interview data the client did not receive a frequency count for the category of *quality*. However the client did demonstrate through other categories, a general understanding of quality, by acknowledging the main regulatory agency involved in the project and their general expectations (CL1-96).

The main contractor's validation category frequency count was substantially higher than that of the client. The main contractor's account of the project resulted in a greater number of specific on-site observations, with some interview question responses based on previous experience of pharmaceutical projects. The client displayed in the interview that they had a large amount of manufacturing equipment validation experience and less experience of validating construction facilities such as HVAC systems (Cl1-411).

Examining the time code categories for each interview it is demonstrated that the timing of the validation activities by both the client and contractor were based on *previous experience* (CL1-TIMEPE-233, C1-TIMEPE-81) and in the case of the main contractor the view was held that the bulk of the validation works would commence in the *commissioning phase* of the project. The client understood that the validation activity should have been started at an early stage of the project but conceded that this probably did not happen. The client did note that the validation activities of the project had not actually been concluded at the time of the interview, citing 'waiting for the odd document' as the main reason. The different views of where the validation activity sits within the overall project task sequences are highlighted by these time category results.

The formal semi-structured interviews were useful in the opening stage of the study, though by conducting formal interviews the interviewee can sometimes be seen as not having a natural role within the setting. The way in which people react and work is influenced by the presence of an observer.
To a certain extent the interviewees may have been subject to a variety of the *Hawthorn Effect*, (as described by Roethlisberger & Dickson, 1939), where the interviewee appears to tell the interviewer what he thinks the interviewer wants to hear. Formal interview techniques were replaced in the later case studies in favour of informal unstructured discussions with informants, followed by note- or record-taking as the main data collection method for the remainder of the fieldwork.

6.10 Case Study A – Participant Observation

6.10.1 Introduction

The data collected from Case Study A is included in appendix B. Individual data sources are numbered A1 to A25, and represent observations, memos, meeting, audit and protocol documents etc. collected during the fieldwork phase of the study. Participant observation of Case Study A was undertaken from June 2000 to June 2001 and analysed under the problematic theme headings derived from the data sources, namely:

- Culture and attitude (Project environment)
- Planning ((time and cost), communication, integration, resource).
- Implementation (control and sequence, change and partnering).
- System Complexity (termination, start-up and commissioning)
- Quality and Regulatory Compliance

6.10.2 Culture and Attitude - project environment

Validation Service Provider (VSP 1)

The validation consultants' work package included validation of the construction systems and the process systems. Validation team members had a variety of professional backgrounds. The validation manager responsible for the validation team was a mechanical engineering graduate and a significant number of the validation team were from a scientific backgrounds relating to either chemistry or biology. The site validation team did not include any construction related personnel. During the early stages of the project the validation consultant relied greatly on the client's quality assurance team to assist them by providing information on the site equipment and utility systems.

For reasons explained later in this account of case study A, the validation service provider's contract was terminated by the client just prior to the site based execution

of the validation works. The client's quality assurance department took responsibility for the validation activity, amended the project validation protocols and completed the on-site testing.

Design& Build Contractor (C 1)

The design and build contractor's experience was wide ranging and the project manager had been involved in the construction of a pharmaceutical manufacturing facilities and had experience of facility validation.

6.10.3 Planning

The VSP produced a schedule of validation works for the client indicating durations for protocol execution. An initial duration of five days was programmed for execution of IQ protocols which the client considered too short, based on their previous experience.

The VSP submitted their validation protocols for client approval in September 2000. The client reviewed the protocols returned them to the VSP with comments and the VSP again resubmitted the documents. At this point the validation consultant stated the protocols were complete and suitable for execution.

This caused the client to question the ability of the VSP and resulted in the generation of an adversarial relationship.

System Identification

The task of plant and systems identification within the pharmaceutical environment is reasonably well understood. Items are generally identified for asset register and/or maintenance purposes and the pharmaceutical organization develops a system to facilitate identification. As previously noted[1]system identification strategies differ between the quality and engineering (construction) disciplines.

One of the major activities associated with the pilot plant construction was that of providing documented evidence, by way of the validation process, that the installation and operation of the main items of process equipment and associated building systems complied with the principles of GMP. A fundamental part of any

[1] See Chapter Two for an explanation of the differing requirements of quality and engineering systems.

installation qualification process is identification. As the construction works of the project neared completion, validation protocol preparation was also virtually complete. A common requirement of IQ protocols is that of providing system documented evidence in the form of drawings. The drawings for a typical HVAC system would include the identification of all quality critical items. The identification process generally includes physical identification which relates the drawing identification and to the installation protocols.

A review of the VSP's installation protocols highlighted that system identification for the new pilot facility had been overlooked (A2) and his had major implications on the progress of the project.

The existing site identification database system was passed to the main contractor to allow for the generation of new system tags. New system numbers were generated and added to the installation drawings, validation protocols and were physically attached, in the form of tags, to the specific items of plant and equipment. This omission put a strain on the main contractor's resources (A9, A10) and caused delay.

6.10.4 Implementation – control, sequence, change, partnering

User Requirement Specification

A User Requirement Specification (URS) was produced by the main contractor during the conceptual design phase of the project and approved by the client's engineering project manager. No other representative of the client, such as the client's quality assurance group, was involved in the approval process. The URS contained general detail regarding the validation requirements of the pilot study and site re-development works.

A copy of the URS was received by the client's validation manager post approval stage. Notable comments were raised at that stage;

> what they are saying is just straight out of the text book and does not give me the assurance that it has been written by someone who has any idea what he is doing..what are the qualifications of the people doing the validation..are they qualified to say what is critical or will they just ask us i.e. have they validation experience in pharmaceuticals?

Functional Specification

A functional specification was not produced until the commissioning stage of the project and was only produced after the client requested a copy.

Validation Master Plan

The site Validation Master Plan was written and approved in 1999 incorporating comments from a multi-disciplinary team. The client also had written a manufacturing centre validation policy document and various Standard Operating Procedures (SOP) for associated activities of critical systems change control, preparation of qualification procedures and plant validation procedures.

Design Qualification

Design Qualification protocols were approved by the client in June 2000 but the progress in completing the execution was limited by the availability of purchasing and design information from the main contractor. The DQ stage was not adequately resourced and incomplete at the time the VSP produced the IQ and OQ project protocols.

Limited design information from the design and build contractor had a negative impact on the quality of the project validation protocols.

Installation Qualification and Operational Qualification

Vital information that was required but not included in the initial installation and operational testing protocols delayed the production of the protocols and resulted in the execution of tests being undertaken in and just prior to the commissioning phase of the project.

Change control

The validation activity needs to be able to cope with changes in the construction process. Variations that occur in the design and installation phases need to be communicated through the project to ensure that the project validation documentation accurately reflects that of the newly constructed facility. The implications of change are often not fully understood by those involved within the

project. Throughout case study A there were numerous items supplied that were different in detail to the initial specification. The lack of specification at design stage leaves the possibility of changes to be made during the construction phase. Control of change[2] necessitates the project team recognise that a change has occurred, asses the impact of the change and record the change. A number of significant changes occurred in the project caused by poor information exchange between the client and main contractor and related to specific process equipment details. Modifications were made to the facilities structural steelwork which resulted in a re-routing of some building services distribution networks. This in turn altered the position of a number of items of plant and critical control sensors.

The associated drawing revisions with these changes were made during the construction phase of the project. The revised project documentation was distributed to the client and the clients engineering project manager acted as the interface between client and the construction project. On occasions, revised project documentation was not forwarded to the client's quality assurance department, who, as a result, were unable to capture project change. The consequent effect was that some of the validation installation tests became an exercise in retrospective validation. Mechanisms for controlling change such as a design approval strategy were not implemented in this construction project.

6.10.5 System Complexity (termination, start-up and commissioning)

The initial validation protocols provided for some testing procedures that were not able to adequately test the installed quality critical systems. The specified space temperature mapping procedure was not based on any traceable standard procedure. The test did not stipulate the type of logging equipment to use and did not give any reference to issues such as calibration.

The complexity of the variable air volume HVAC system (A6) was such that the operation and maintenance aspects of the system were not well understood by the installer and validation service provider. Testing documentation did not include tests

[2] See section 3.11

that were of sufficient detail to confirm that a suitable system had been installed. Operational tests proved that conditions could be controlled within an acceptable range were not executed. Test procedures using single environmental parameter readings of temperature and humidity did provide evidence that on the day of test the system was operating satisfactorily. The problem with this type of test was that the system was not stressed in any way by being subject to a range of test conditions. Communications and information exchange problems between project groups relating to the process systems had a major affect on the project schedule. The way in which process equipment was to be integrated into the facility suffered from both the clients and main contractors understanding of new technologies. The integration and assessment of the success of this new manufacturing equipment was one of the major objectives of the pilot plant. The new equipment had neither been tried nor tested in both installation and operation and the client was unfamiliar with the machinery. The main contractor advised that this lack of understanding had an impact on accommodating the equipment within the facility. The resultant outcome from this complexity issue caused the validation activity to suffer due to continual changes to the structure and services.

Commissioning

The commissioning phase of the project is typically where the building and systems are tested and put into operation. Validation of the critical main building systems is also undertaken.

The commissioning tests indicated functionality and the commissioning contractor considered that at this stage sufficient evidence has been provided that the project was finished and ready to hand over.

Prior to the commissioning of the project there was no clear lines of communication between the client's QA validation group and the main contractors designated commissioning manager. Some validation tests were carried out in isolation and not witnessed by the client's validation department (A 16). Repeat testing was undertaken at the request of the client that resulted in an additional cost and delay for the main contractor.

The commissioning contractor documented the repeat tests together with all other commissioning tests and this was included in the main contractors Operation and Maintenance (O&M) manual. Specific details documented in the O&M

documentation relating to instrument calibration, equipment certification, measurement procedures and as fitted drawings were also needed to complete and close out the validation protocols. This essential information was not obtained until December 2000, after all site activities were completed (A18) and caused a delay in issuing the pilot plant validation completion certificate.

6.10.6 Quality and Regulatory Compliance

Validation Documentation

The interpretation and compliance to current GMP standards is demonstrated through validation tests. The installation and operational testing phases have been identified in the literature as being those areas that the project team have greatest influence over. The validation IQ and OQ protocols were written by VSP1 and were submitted for approval to the client. The client reviewed the facility validation package and observed that the documentation was not suitable for use (A1- 18, 73). The content of the protocols indicated that the author was unfamiliar with construction and building services systems and the application of GMP to these system types.
The specific areas where the installation qualification deviated from the recommendations of the literature are as follows:

Identification

The IQ protocol document did not provide any formal means of identifying individual components or pieces of equipment (A20-73). The fundamentals of installation qualification rely on the cyclic process of identification and comparison.

Testing Rational

The methodology, by which the installed identified item was compared to expected installed item, was not included in the documentation. Regulatory Agencies require that a traceable audit trail exist to allow clear unambiguous assessment of the process.

Materials of Construction

Although the manufactured drug product would not normally come into contact with the constructional components of a manufacturing facility as it would do with the

manufacturing process, it is recommended by the FDA that the details of materials of construction are obtained from the vendor. This information would be included in a validation protocol used to confirm that the facility has been constructed in line with the regulatory requirements. The regulatory requirements do not specify composition requirements of materials, only physical attributes of surfaces and room size, e.g. it is suggested floors, walls and ceilings have smooth hard surfaces that are easily cleanable.

The IQ documentation produced by VSP1 did not include a construction materials section (A20).

Maintenance

As previously noted in Chapter Three, premises maintenance operations that present a hazard to the product quality are required to comply with GMP. The validation consultant's IQ did not include a maintenance section.

Critical Equipment

Within the IQ protocol a number of quality critical[3] items were included, such as equipment installed to monitor the room pressure differentials between the classified space and adjacent circulatory space. The level of detail given in the documentation relating to these pressure sensors was minimal and information such as a vendor's model number was not included in the documentation. Sufficient detail should be provided to allow a connection to be made between the IQ and OQ process stages. In this instance OQ validation follows IQ validation, the identification and confirmation of the installed device's model number would have displayed that the devices model number related to an operational range providing another level of assurance, other than a unique identifier tag, that the item was as 'design' and suitable for its intended use.

During the case study, occasionally an item, would be installed and validated, and during the operational validation checks, would fail to meet the acceptance criteria set out in the protocol.

Included in the installation qualification were a number of items that would normally be classified as indirect, having no effect on product quality, and therefore would

[3] See section 3.3 for an explanation of quality critical items.

not require qualification. Electrical distribution panels were included in this section and test acceptance criteria of 'the panel is clean and tidy' (A20) underlined the protocol author's misinterpretation of the projects validation requirements.
Critical system components like terminal high efficiency air filter that are central to achieving the clean room classification levels of production environments, were not included in the installation confirmation. Filtration tests were included in the operational confirmation documentation; but there were no acceptance criteria (A23).

System Descriptions

In any validation protocol, understanding and knowledge of the system is demonstrated by the inclusion of a system description. This permits the reader (auditor or inspector) to gain an appreciation of the details of the system and displays that the author understands the system, functions and quality related attributes.
The opening description of the HVAC installation document did not mention and sufficiently explain a number of the major critical system components (A20).
Some items of HVAC equipment included in the description were not included within the installation confirmation section.

Protocol Format

The protocol documentation format appeared to be based around the template that would normally be adopted for a piece of manufacturing equipment (A21). Test descriptions were single line statements and were actually a statement of acceptance rather than test descriptions. Where acceptance criteria were stated, in some cases, the criteria were not related to a named test standard. The application of testing standards allows the document reader to asses the suitability of the testing methodology.
Measurement tolerances for tests were included in a number of the validation tests but no reference was made to testing and commissioning codes of practice, such as those published by the Chartered Institution of Building Services Engineers (CIBSE) in the UK and the American Society of Heating Refrigeration and Air conditioning Engineers (ASHRAE) in the USA.

Direct and Indirect Classifications

The testing protocols made little distinction between impact classifications and criticality of systems. System testing procedures, with respect to installed environmental monitoring systems, did not relate to the main focus of GMP, i.e. the product. In the event of a room pressurization failure, and hence loss of product containment, the operator is notified by an alarm and stops production. The validation test document for room monitoring functions focused on plant room alarms related to items such as air handling units rather than the manufacturing production space.

The adopted approach to writing validation protocols clearly demonstrated a limited knowledge of GMP principles and construction systems.

Criticality & Calibration

The installed systems which are used to control and monitor the production environment within the pilot facility consist of critical systems components such as gauges, detectors and alarm systems. The project team were unsure about which items would require calibration (A9, A11) and the views held between the construction organization and client differed greatly. The main contractor suggested that all sensors and similar items would be factory calibrated and installed ready for operation. Following installation, the system would be commissioned and handed-over. The client's engineering project manager was also of the impression that building services instrumentation should not be calibrated (A11). The project manager was aware that the controls specialist may have calibrated 'some' of the instrumentation during commissioning but conceded that there may have be some procedural differences between quality assurance and construction contractual requirements. As a result, a meeting was held with the client's metrology department and a classification strategy was implemented. A critical instrument assessment was undertaken with the validation service provider to classify instrumentation as critical and non-critical. Only those items deemed critical were calibrated and entered onto the client's site calibration register. This situation would have been avoided, if at the initial stages of the validation activity, a critical instrument assessment had been carried out and included in the installation qualification protocol.

At this point in the project no Standard Operating Procedure (SOP) for calibration was written (A4, A19).

6.10.7 Semiotic Data Analysis

To determine the frequency and importance of emergent themes a *project code matrix* was constructed from data sources A1 to A25. A *semiotic data analysis* was then undertaken of the main data A1 to A25, a critical activities memo (A) and finally of all data sources derived from the case study. The *multiple code frequency searches* of the data files were conducted using manual techniques[4]. Figure 6.12 shows the project code matrix and figures 6.10 & 6.11, show the semiotic data analysis of a critical activities memorandum (A) and case study data A1 to A25.

Figure 6.10: Case Study A Semiotic Analysis of Data A1 to A25

Code Group	Code Frequency	Code Percentage (%)
Complexity	3	6.8
Contract	0	0
Cost	0	0
Experience	7	15.9
Implementation	7	15.9
Implementation Model	2	4.5
Partnering	0	0
Quality	2	4.5
Termination	1	2.27
Time	3	6.8
Validation	19	43.1

Figure 6.11: Semiotic Analysis of Critical Activities Memo Data

memo – A		
Code Group	Code Frequency	Code Percentage (%)
Complexity	1	8.3
Contract	0	0
Cost	0	0
Experience	3	25
Implementation	2	16.6
Implementation Model	0	0
Partnering	0	0
Quality	1	8.3
Termination	0	0
Time	3	25
Validation	2	8

[4] Manual techniques were used here since the majority of data were not in the form of electronic documentation.

Figure 6.12: Project Code Matrix – Qualitative Data

Code Family / Data Ref.	Complexity	Contract	Cost	Experience	Implementa	Implmodel	Partnering	Quality	Termination	Time	Validation
A1.	X	X	X	18,18	X	X	X	X	X	X	73
A2.	X	X	X	X	X	X	X	X	X	X	87
A3.	X	X	X	X	22,29	X	X	X	X	X	76
A4.	X	X	X	X	X	X	X	X	X	X	63
A5.	X	X	X	X	X	X	X	X	X	X	83,87
A6.	X	X	X	18	27	X	X	X	X	X	70
A7.	X	X	X	18	X	X	X	X	X	X	83
A8.	X	X	X	X	X	X	X	X	48	X	X
A9.	X	X	X	X	30	X	X	X	X	X	88
A10.	X	X	X	X	30	X	X	X	X	X	X
A11.	X	X	X	X	X	X	X	X	X	52	87
A12.	X	X	X	X	X	X	X	X	X	49	X
A13.	X	X	X	X	X	X	X	45	X	X	X
A14.	6	X	X	X	X	X	X	45	X	X	X
A15.	2	X	X	X	X	X	X	X	X	X	X

Figure 6.12 (Continued): Project Code Matrix – Qualitative Data

Code Family / Data Ref.	Complexity	Contract	Cost	Experience	Implementa	Implmodel	Partnering	Quality	Termination	Time	Validation
A16.	X	X	X	X	30	X	X	X	X	X	70
A17.	X	X	X	X	X	X	X	X	X	X	87
A18.	X	X	X	X	X	X	X	X	X	X	87,88
A19.	X	X	X	X	X	X	X	X	X	X	79,86
A20.	X	X	X	X	X	33	X	X	X	X	73
A21.	X	X	X	X	X	X	X	X	X	X	76
A22.	X	X	X	18	X	33	X	X	X	X	X
A23.	X	X	X	18	X	X	X	X	X	X	X
A24.	X	X	X	18	X	X	X	X	X	X	X
A25.	02	X	X	X	52	X	X	X	X	49	70

6.11 Discussion

The main objectives of the pilot case study were to obtain qualitative data sets from two main orientation sources. A fieldwork study was used that employed observation and sensitising interviews with the design and build contractor (C1) and client validation manager (C11). The code categorizations that emerged generated a *three level code family tree*, indicating parent and child levels. The *theme classifications* were then used to code and theoretically sample the qualitative data from the next stages of fieldwork.

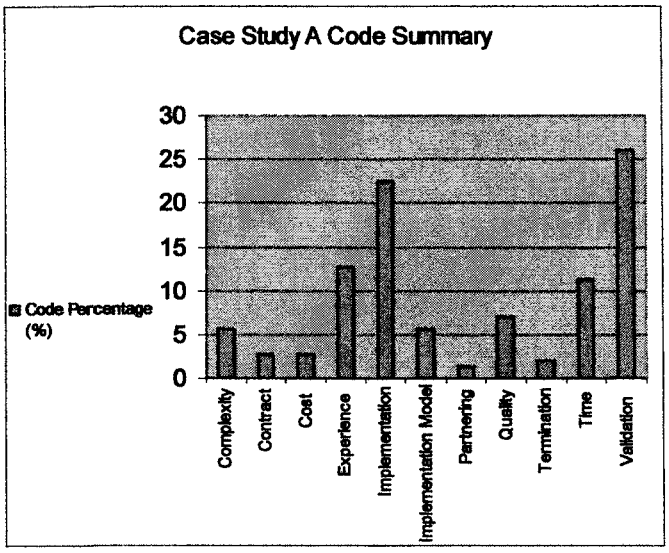
Participant observation of Case Study A was made prior to the sensitising interviews and the data from the observation study was re-coded in line with the outcomes of the initial orientation research. The quality and quantity of the information that resulted from the observation fieldwork supported the continued use of the research methodology. Whilst formal interviews are useful in sampling the views and attitudes of the informants, they are conducted in an unnatural and controlled environment and can be influenced by the interviewer being seen as an outsider. Therefore, they were not utilized in subsequent fieldwork.

Categories that emerged from all case study data sets are tabulated below in figure 6.13 and displayed in figure 6.14.

Figure 6.13: Semiotic Analysis Summary (all Data)

All Data		
Code Group	**Code Frequency**	**Code Percentage (%)**
Complexity	8	5.6
Contract	4	2.8
Cost	4	2.8
Experience	18	12.67
Implementation	32	22.53
Implementation Model	8	5.6
Partnering	2	1.4
Quality	10	7.0
Termination	3	2.11
Time	16	11.26
Validation	37	26.05

Figure 6.14: Semiotic Analysis Summary



As shown in Figures 6.13 and 6.14, a number of particular important themes emerged from the data which relate to the study propositions. Observations with the highest frequency counts were in the *experience* (12.67%), *implementation* (22.53%), validation (new emergent code) (26.05%), *quality* (7%) and *time* (11.26%) categories. Relating this data to the study propositions, Figure 6.14 displays that at least one of the theoretical validation themes that relate to study propositions, P1 to P5, was observed in the field.

Whilst the case study observation data content corresponds to the common emergent themes of those from the interviews, there are also some differences. Continued observation over a sustained period of involvement in the project environment has resulted in a greater percentage of observations relating to specific validation and implementation issues. Freedom of access and the development of good working relationships with participants were key contributory factors to the success of theoretical sampling.

6.11.1 Culture and Attitude (project environment)

The case study highlighted that the validation process was sat within the environmental boundaries of both the construction and pharmaceutical organizations.

Initially it was unclear where the validation service provider was positioned in terms of the theoretical systems model, but it later emerged that the VSP's background and experience was aligned with that of the pharmaceutical industry and not construction. The client's appointed VSP was unable to successfully provide system process input, in the form of validation protocols, in a consistent and timely manner.
As the relationship between the client and VSP deteriorated the client became responsible for all validation execution and the system environmental boundary shifted bringing the design and build contractor further into the task environment. The limited flexibility of interfacing sub-systems and cultural differences of the groups negatively impacted on the progress of the project.
The validation process system reacted as an open system, meaning that the system received inputs and transformed them into outputs. The validation process on a number of occasions represented a closed or black box where the transformation process produced little in the way of output.

6.11.2 Planning ((time and cost), communication, integration, resource).

The planning processes suffered from what the client regarded as inaccurate estimates for completing the site-based validation works. There was no clear example of how the VSP estimated time/cost schedules and the late submission of testing documentation indicated whatever method that was used was inaccurate.

6.11.3 Implementation (control and sequence, change and partnering).

Analysing the sequential sub-process of the validation activity, by utilizing pattern matching, established that there were deviations from the cybernetic model.
Firstly, the user requirement was not produced by a multi-disciplinary team and was subject to retrospective review by the client's quality assurance group. The project progressed without a functional specification until late into the operational testing and commissioning phases. This deviates from the fundamental purposes of pre-qualification activities suggested by the literature review.
The design review stage was not adequately resourced and incomplete at the time of commencement of installation and operational testing, again deviating from the model.

IQ and OQ document production was delayed as a result of communications problems between the client and the VSP. As a result there was a delay to the site testing phase which impacted on the commissioning phase.
Control procedures were inadequate because time delays influenced the sensing function of the model and meant that protocols were not fully developed. Lack of understanding and adoption of adequate testing standards, employed in the protocols, initially producing inaccurate cybernetic control. This indicated that the model feedback loop was strongly influenced by human interaction and so displayed problems associated with third-order systems. The site execution process, by the clients QA staff and main contractor stabilized the system through increased control.

6.11.4 System Complexity (termination, start-up and commissioning)

Many of the building HVAC systems were inadequately tested due to limited understanding and operational data. The presence of building system complexity was demonstrated by both the installer and end users in their lack of operational understanding.
Complexity was also shown by inferior testing documentation which did not provide system testing of all critical functions and across the full operational range of the plant.
The level of technical sophistication of the manufacturing equipment and its interface in the project environment also provided specific procurement and integration problems.

6.11.5 Quality and Regulatory Compliance

Major critical omissions were made in the IQ and OQ testing protocols. A significant problematic theme emerged from all data sources and greatly added to the understanding of the validation process. The ability to correctly identify and label quality related facility systems was inadequately controlled and directly impacted on the IQ stage of the process model.
The sensitising interviews and case study analysis were carried out to asses 1) the data collection method as an instrument for use in the main case studies 2) to clarify, corroborate and focus attention on the specific developing study propositions and categorizations – operationalisation and 3) provide, by a grounded theory-like methodology, a multi-level code family tree to use in subsequent case studies.

Through the application of the orientation technique of sensitising a multi-category family tree has successfully emerged from the data. The emergent categories have been given unique identifiers which link the software code book to the numbered family tree.

The data collection and analysis method has contributed to the procedure of operationalization and to continue this process, the generated data can now be used to observe further case studies, with the goal of empirically testing those theories that have been developed thus far. Analysis of the validation process model over time has so far indicated deviations in model sub-process sequences.

The next Case Study, Case B, uses the code categorizations that emerged from Case Study A, represented by a three level code family tree, to code and theoretically sample the second data set B. This data set will then be used for data set analysis and comparison.

Chapter Seven: Case Study B – Results and Analysis

The second of the case studies is presented in-line with the case study methodology outlined in Chapter Five and provides qualitative case study evidence from case study B.

Code categorizations that emerged from the orientation and theoretical sampling phases of Case Study A, represented by the three level code family tree, are used to code and theoretically sample the second data set derived from case study B.

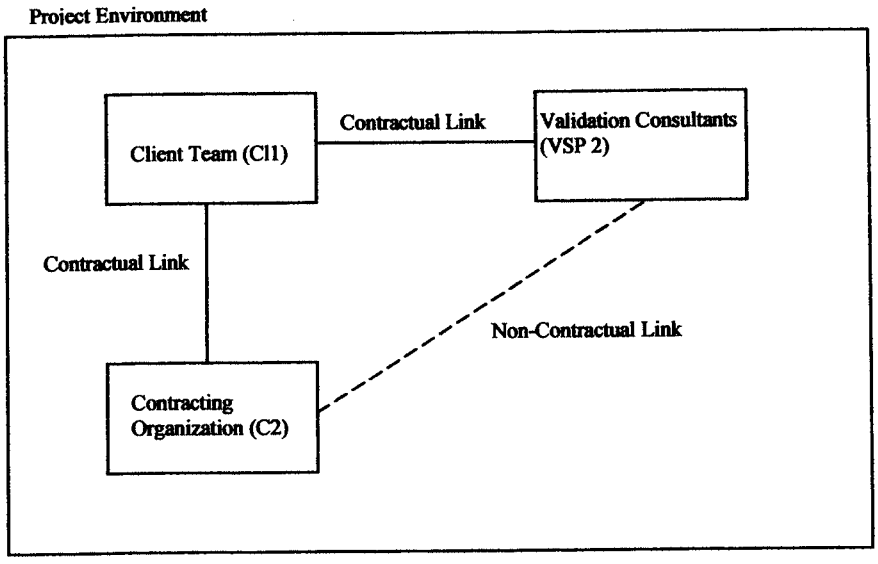
The results for this second case study are presented and analysed.

7.1 Project Description

The project involved the construction of a pharmaceutical dispensing facility. The dispensary was to consist of a number of dispensing suites, each with materials and personnel airlocks and dispensing rooms which housed down flow dispensing booths. The dispensary project was part of the on-going site re-development and was constructed on the site of a demolished production area centrally located within the manufacturing site. This area is referred to in the study as the 'central core' area. The construction project had an initial construction programme duration of eleven months (October 2001 to September 2002).

The construction management project had the following structure:

Figure 7.1: Case Study B Project Environment



The main groups involved in the project were the client (Cl1), construction management contractor (C2) and the Validation Service Provider (VSP2).
The client organization team consisted of quality assurance, production, packaging, logistics, engineering, health and safety, purchasing and finance departments. Additionally, an engineering project manager was seconded to the project from one of the client's other overseas sites. The main contracting organization was a national construction company, with its head office based in the south east of England. The contractors business activities were general construction. Validation services were provided by the validation sector of a UK based commissioning contractor also located in the south east of England.

In line with case study A, analysis is based on the problematic theme headings derived from the literature, namely:

- Culture and attitude (project environment)
- Planning ((time and cost), communication, integration, resource).
- Implementation (control and sequence, change and partnering).
- System Complexity (termination, start-up and commissioning)
- Quality and Regulatory Compliance

7.2 Culture and Attitude (project environment)

Validation Service Provider 2

Commissioning and validation of the dispensaries were the responsibility of a single organization that had contractual ties with the main contractor for commissioning and the client for validation. The validation service provider's work package included validation of the dispensary building systems and associated utilities including HVAC, purified water, room monitoring systems and construction of the dispensary rooms. All equipment and process systems were validated in-house by the client.

The commissioning and validation team members had backgrounds in mechanical and general building services engineering. The validation manager responsible for the validation team was a chartered mechanical engineer who had validation experience in pharmaceutical and sterile manufacture although the core business of the validation organization was commissioning of mechanical building systems. The contractual format was such that occasionally validation tasks were undertaken by the commissioning team and visa-versa.

Main Contractor 2

Whilst the main contractor's experience was wide ranging, only a small number of the key managers had been involved in the construction of a pharmaceutical manufacturing facility. However, recent projects including microelectronic clean room manufacture had impressed the client persuading them to appoint the construction organization as main contractor for the remainder of the site development construction projects.

Architect and Building Services Engineering Consultant

The project architect was located close to the project site and had previous experience of designing pharmaceutical manufacturing buildings. Previous experience had included assignments in the UK and overseas for large pharmaceutical manufacturers. Engineering services were provided by a services consultant from Yorkshire UK. The building services engineer had designed HVAC systems for a substantial number of pharmaceutical facilities. Occasionally, in the past both the architect and engineer had formed partnering alliances to offer specialist 'clean' manufacturing expertise to clients.

As part of the site re-development, the client's quality assurance department was implementing a central GMP upgrade project. The aim of the project was to guarantee alignment of the upgraded facility ensuring continued compliance with GMP and to support procedures, flows and dust containment up to international standards.

The key requirements for achieving the objectives such as regulatory compliance, validation and environmental control, were well defined and are included in Appendix B. (B2 and B3).

7.3 Planning

A check matrix (B20) for central core fabric and environmental validation was constructed by the client. The check matrix approach tabulated the levels of validation activities required against the new systems that were to be installed. The matrix approach is a comparison of the types of systems that exist within a facility. The amount of validation testing is dependant on the criticality and complexity of the system. Critical systems may not always be complex; likewise complex systems may not always be critical. Complex critical systems will require validation tests that sufficiently demonstrate the operation of the system complies with only those aspects of GMP that are system critical.

System Identification

Not all items of plant were identified prior to the IQ works which caused confusion for the validation consultant. The identification relied on the building services engineer producing amended drawings for the main contractor to utilize in ascertaining equipment identification. The final positioning of tag identification was the main contractor's responsibility who occasionally failed to attach a tag or identified the wrong piece of plant (B13).

7.4 Implementation – control, sequence, change and partnering

User Requirement Specification

A User Requirement Specification was written for the site re-development project and approved in October 2001. In line with chapter 3, a multi-disciplinary team was involved in the production of the document. Representatives of the clients engineering, production, quality assurance, product transfers and health, safety and environment departments were signatories to the document approval.

The specification deviated from recommendations outlined by commentators such as Wingate (1997) only proving limited specific information on validation of building systems in terms of building fabric and environmental requirements.

Functional Specification

Figure 7.2, illustrates that a functional specification was not produced for the dispensary project. As part of the clients design qualification validation an action plan of GMP deviations was constructed which highlighted the fact a project FS had not been used in the validation process.

Figure 7.2: Design Qualification Actions

Action required	Responsibility	Timescale	Status
Functional Specification			
A FS does not exist. Check building services engineer and C2 files to investigate if there is any documentation which could be used as a functional specification.	Cl1-Validation	15/10/03	Action plan issued 30/09/03. All actions ongoing

Validation Master Plan

The Validation Master Plan for the site re-development project was approved in December 2001. Again, a multi-disciplinary team was involved in the production of the document with representatives of the client's engineering, production, quality assurance, product transfers and health, safety and environment departments as signatories to the document approval.

Design Qualification

A design review was completed in September 2003, some nine months after the end of the validation project reflecting a time series deviation from the cybernetic model.

Installation Qualification

Validation Service Provider 2 produced installation qualification documents for the building systems of the project in November 2002. The installation qualification was executed in December 2002.

Operational Qualification

Validation Service Provider 2 produced operational qualifications for the building systems of the project in November 2002. The protocol was executed in late November and December 2002.

Change control

A number of significant changes occurred to building services systems, which may have been avoided if a design review had been carried out by the project team at the correct stage in the project.

Air conditioning systems serving the materials and personnel air lock to each dispensary did not contain sufficient levels of filtration and as a result could not achieve the correct room classification. This deviation was discovered by the validation team prior to the approval of the validation protocols. There were also GMP omissions in the form of room monitoring and alarm systems and positioning of critical system control detectors.

During the execution of the IQ the validation team noticed that the critical room temperature probes had been installed in the supply ductwork instead of the extract ductwork. In that position the detectors could not control the environment satisfactorily and repositioning was required. This represented a failure in the IQ test acceptance criteria which was pointed out to the controls contractor who then rectified the situation. The change was considered minor as the remedial works of the change were carried out instantaneously and prior to system start up. The particular type of temperature probe used, however, did cause some problems. There was no initial project input by the client calibration department or the VSP in identifying the suitability of instrumentation in terms of calibration procedures and identifying quality critical instrumentation. It was discovered at IQ stage that detector site calibration was not possible and would require that the detectors be taken off site to be calibrated. This posed a large problem for the client and resulted in a change to the type of sensor installed for such a critical task.

The client had devised a design approval change system as a procedure for accommodating major project changes (B1). The change system permitted the deviation between actual and expected deviation to be classified as either major or minor. This simplified the validation system steering process which helped a decision to be made on corrective actions.

Occasionally, revised project documentation was not distributed to the client's quality assurance department, who, as a result were unable to capture project change. Some of the deviations were not therefore discovered until IQ stage.
VSP 2 and the client produced a plan of validation works indicating durations for protocol execution. Initial durations of ten days each were programmed for execution of the IQ and OQ protocols execution.

Validation Protocol Execution

The construction and hand-over of the dispensary was delayed because of the discovery and need for removal of a large quantity of asbestos in the area that was to become the new dispensary (B7). Other reasons for delays were mainly related to communications and information flow problems between the client and the construction team (B8). Decisions were still being made by the client, several months after the start of construction, about the choice of ceilings and floor toppings. The engineering department was under-resourced and struggling to cope with day to day maintenance of the whole facility whilst assisting the project team in the provision of the new dispensary building.
There was no Validation Master Plan (VMP) produced for the project works until December 2001, after the commencement of the project. The facility was initially to be handed over in September 2002 and a revised date of 8th November 2002 was set. Validation IQ and OQ protocols were still being prepared in October and November 2002.
The validation certificate of completion was signed on the second of December 2002 but at that time there were still a number of outstanding validation items to be completed (B13).

Common problems associated in completing the validation works were:

1. Red-lined construction drawings were used during validation since the approved as-built drawings had not been supplied. Approved schematic diagrams that are required for the installation qualification testing were not available until after the contractor handed over the facility.

2. The O&M manuals listed in the protocols were not submitted to the client prior to handover. This delayed completion of the validation protocols.

3. At the time of dispensary handover, the process of producing and approving maintenance records was not complete e.g. Section 11. Attachment 2. PMI 06MDHUALSERV for the 6th monthly service of the dehumidifier was not approved.

4. The validation service provider did not complete the witness/approval signatures on the commissioning validation document.

5. HVAC system components which were not fully identified during the project were only tagged during routine maintenance procedures up to ten months after completion. This required communications between the client's engineering maintenance department and QA department so that the client's validation group could update their record files.

6) Missing identification for critical plant and equipment.

7) Incomplete direct impact component calibrations.

8) No 'true' verification procedures in place.

9) Validation tests being completed post handover certification. i.e. temperature mapping.

As suggested in Chapter Two maintenance procedures for critical components and systems are required to be provided as part of installation validation. Maintenance along with cleaning is considered essential in providing a compliant environment. Systems that receive regular maintenance and cleaning are less likely to have an adverse effect on product quality. Maintenance procedures and schedules are included within the validation package to demonstrate that there is a system in place and it complies with recommended planned maintenance procedures of the system vendor. During the execution of the IQ protocol the validation consultant advised the

client that he was unable to complete this section of the documentation because maintenance details were not available for new items of plant and equipment. The production of this significant quantity of information was the responsibility of the site maintenance manager who had up until this point had little involvement with the project. The client's maintenance resource was stretched and the slow production of schedules started to delay the installation qualification task. As a result, extra resource was made available to help to complete the schedules and the sequential process was such that maintenance data had to be available and approved to permit completion of the validation IQ and OQ stages.

7.5 System Complexity (termination, start-up and commissioning)

The validation documents provided a very basic level of system test coverage. The first versions of the test protocols submitted to the client were not appropriate to the system. A number of items, which had a direct system impact, were missed out of the documentation (B16) and some test standards to be applied had been superseded and were incorrect for the type of test required. The installation of the down flow dispensing booths caused conflict with the dispensary HVAC systems. The building services consultant did not take into account the effect the down flow booth would have on the facility airflow patterns and pressure differentials. This in turn affected the outcomes of the operational validation, with a number of tests failing to meet there acceptance criteria.

To rectify the situation, the commissioning engineer had to embark on a lengthy re-balance of the dispensary air distribution system. In addition, there were problems of construction in the dispensaries, such as large gaps left around doors, light fittings and some items of 'built-in' manufacturing equipment. Consequentially there were excessive air leakage rates and the acceptance criteria for room ventilation rates were not being achieved in the validation protocols. The remedial works for the main contractor were protracted and delayed the final HVAC commissioning and validation process.

Project Termination

The MCA (or MHRA as it is now called) were invited to site in July 2002 for informal discussions with the client's quality assurance and engineering directors. The site meetings and informal review of site re-development plans were seen, by the client, as a way of obtaining assurance that the strategies for the site upgrade works were in-line with current GMP. During the two day attendance, the agency representative suggested that the client needed to re-assess its site strategy for product containment and its methods of monitoring containment in the new facilities. The regulator felt that there was an insufficient level of monitoring systems incorporated into the plant design.

Qualitative data codes sheet B22 is a record of a post project audit carried out by the client's quality assurance group. The audit was carried out in January 2003 and highlighted a number of possible GMP non-compliance issues.
Design Qualification or as it was termed, design review, was considered as an after-thought and was not completed until December 2003 (B21). The opportunity to provide control measures at design stage, to include GMP in the design, was effectively lost.
Resulting compliance issues related to environmental monitoring, room luminance levels, and calibration of temperature probes. Instrument criticality assessments had not been carried out during the project but at post IQ stage. The sensors referred to in qualitative data sheet B22 were assessed and were deemed to be critical.
Measurement of lighting levels within the facility had not been included in any of the project protocols even though this is a requirement of current regulations.

After completion of the project there were still outstanding documentation issues relating to IQ and OQ completion, due to missing document signatures (B 19). A certificate of validation completion had been issued even though the facility was not fully validated. After the project was completed the client produced a review of the validation exercise. Figure 7.3 shows a section of the review.

Figure 7.3: Validation Review

Qualification documents covered by this review

Document Reference	Contents
IA-1166-1	1. Instrument assessment list, system 04/01 • Approved 14 Dec 02
IA-1166-2	2. Instrument assessment list (04/02) revised after addition of new temperature probes • Approved 21 Jul 03
IQP-1166-1 and IQR-1166-1	3. Installation qualification, system 04/01 • Protocol approved 10 Dec 02 • Report Approved 17 Dec 02
IQP-1166-2 and IQR-1166-2	4. Installation qualification, system 04/01, revised after addition of HEPA filtration to dehumidification units. • Protocol approved 23 Dec 02 • Report approved 21 Jul 03
OQP-1166-1 and OQR-1166-1	5. Operational qualification, system 04/01 • Protocol approved 27 Nov 02 • Report approved 16 Dec 02
OQP-1166-2 and OQR-1166-2	6. Operational qualification, system 04/01, after addition of HEPA filtration to dehumidification units. • Protocol approved 20 Dec 02 • Report approved 21 Jul 03
IQP-1214-1 and IQR-1214-1	7. Installation and operational qualification of the environmental monitoring system in the central core (systems 04/01 and 04/02) • Protocols approved 10 Dec 02 • Reports approved 16/17 Dec 02
OQP-1214-1 and OQR-1214-1	

Figure 7.3 clearly shows the very late production and consideration of the facility validation activity. The assessment and production of a critical instrument list was carried out almost in the final days of the validation works. The task should have been addressed much earlier in the project. The installation qualification was revised and re-issued to include new filtration levels to the de-humidification system. If a design review had been formally undertaken, and including all relevant GMP experts, this issue would have been resolved prior to installation and subsequent

project problems and delays would have been avoided. Other notable points are that the Operational qualification documentation was approved before the installation qualification documentation and the final reports for the second version of the HVAC validation were not approved until July 2003. This is not in line with the current best practice literature produced by the ISPE.

In a presentation by the site manager, following the completion of the dispensary project, the client site manager summed up the main problems that had been encountered. The dispensary project and site re-development works were late because of a collection of general project management related problems. Monitoring and reporting functions were not adequate and the client was not able to gain a true picture of the progress. The client displayed limited understanding of the activities of the main contractor who appeared to the client site manager to be running the project. The site re-development budget was stretched and cost forecasting proved to be difficult. Lack of resource and communications deficiencies were cited as the primary reasons for poor control over finance and programmes.

The client realised that additional skilled resources were required. Dedicated resources, attached to sub-projects, were seen as a key area where improvement could be made (B11). The observed monitoring and reporting problems were connected with poor communications between groups, partly due to the lack of attendance at detailed meetings (B7). These control problems were observed in the project environment, partly as a consequence of the different interfacing sub-cultures.

7.6 Quality and Regulatory Compliance

Documentation

VSP 2 submitted their validation protocols for client approval in late October 2002. The client reviewed the protocols and returned them to the VSP with comments. The client's review of the facility validation package highlighted a number of documentation problems. The content of the protocols indicated that the author of the protocols did not appear to understand some aspects of GMP.

The specific areas where the installation qualification deviated from the recommendations of the literature were as follows:

Identification

Again, the IQ protocol document did not provide full identification of individual components or pieces of equipment (B17). The requirements of the client were not effectively communicated to the building services engineer and design drawings did not show tag identifiers. The client had initially requested 'Provision of support documentation for Validation requirements' in the invitation to tender for detailed design (B10). However, this was not discovered until the VSP started producing validation protocols and requested equipment identification details.

The building services engineer considered that it was not his task to generate system and component identification tags, but reluctantly agreed to add the additional detail to his contract documentation (drawings and schedules) at no extra cost. The main contractor had the additional pressure placed on him to provide physical tags and attach them to the equipment.

Testing Rational

VSP 2 requested a copy of typical site validation protocols prior to producing the validation package. Operational testing rational was based entirely based on previous protocols produced by VSP 1 and discussed in case study A. VSP 2 applied a simple 'cut and paste' technique to writing the validation protocols for the dispensary project. No additional testing was added to the basic shell provided by the client and this demonstrated that they were produced by an inexperienced protocol writer.

Direct and Indirect Classifications

The IQ protocol did not differentiate between critical and non-critical equipment. Items that were critical and of direct impact on the quality of the product were missed out of the protocol. Distinctions between impact classifications were not made and system testing procedures were not fully developed.

The adopted approach to writing validation protocols, again, clearly demonstrated a limited knowledge of GMP principles.

7.7 Semiotic Data Analysis

To determine the frequency and importance of emergent themes a project code matrix was constructed from data sources B1 to B22. A semiotic data analysis was then undertaken of the data and multiple code frequency searches of the data files were conducted using manual techniques. Figure 7.4 shows the project code matrix and figures 7.5 and 7.6 show the semiotic data analysis.

Figure 7.4: Project Code Matrix

Code Family / Data Ref.	Complexity	Contract	Cost	Experience	Implementa	Implmodel	Partnering	Quality	Termination	Time	Validation
B1.	X	X	X	X	X	X	X	45	X	X	X
B2.	X	X	X	X	X	X	X	40,41,42, 42	X	X	X
B3.	X	X	X	X	X	X	X	42	X	X	X
B4.	X	X	X	18	28,30	X	X	X	X	X	X
B5.	X	X	X	19	22, 22,27,23,23	X	X	X	X	X	84
B6.	5	X	X	X	29,29	X	X	X	X	X	83
B7.	X	X	X	X	28,28	X	X	X	X	52,49	X
B8.	X	X	X	X	22,22	X	X	X	X	X	X
B9.	X	X	X	X	28,28,30,21,21	32	X	45,45	X	49	87
B10.	X	X	X	X	X	X	X	X	X	X	86
B11.	2	X	X	X	24,24,28	31	X	X	X	X	X
B12.	X	X	X	X	X	X	X	X	X	X	73
B13.	X	X	X	X	29,29	X	X	X	X	52	63,87
B14.	X	X	X	X	30	X	X	X	X	X	X
B15.	X	X	X	18	X	X	X	X	X	X	88

Table 7.4 (Continued): Project Code Matrix

Code Family / Data Ref.	Complexity	Contract	Cost	Experience	Implementa	Implmodel	Partnering	Quality	Terminatio	Time	Validation
B16.	X	X	X	18	X	X	X	X	X	X	88
B17.	X	X	X	X	X	X	X	X	X	X	87
B18.	X	X	X	X	X	X	X	X	X	X	86
B19.	X	X	X	X	X	X	X	X	X	X	86
B20.	X	X	X	19	X	X	X	X	X	X	X
B21.	X	X	X	X	X	X	X	X	X	51	68
B22.	X	X	X	X	30	X	X	45	48	X	X

7.8 Discussion

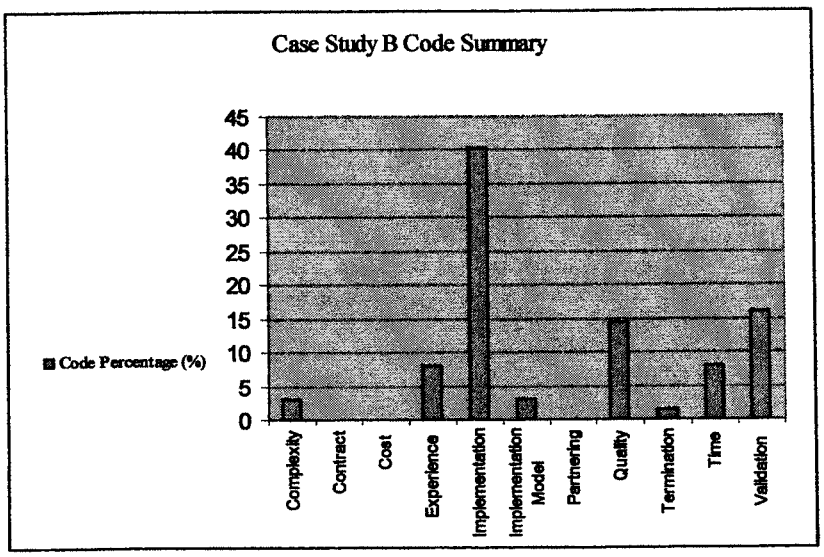
Categories that emerged from the case study data set are tabulated below in figure 7.5 and displayed in figure 7.6.

Figure 7.5: Case Study B – Semiotic Analysis of data B1 to B22

Code Group	Code Frequency	Code Percentage (%)
Complexity	2	3.2
Contract	0	0
Cost	0	0
Experience	5	8
Implementation	25	40.3
Implementation Model	2	3.2
Partnering	0	0
Quality	9	14.51
Termination	1	1.6
Time	5	8
Validation	13	16.12

With reference to figures 7.5 and 7.6, the data presented displays an emergence of a number of particular important themes which relate to the study propositions. Observations with the highest frequency counts were in the experience (8%), implementation (40.3%), validation (new emergent code) (16.12%), quality (14.51%) and time (8%) categories. Relating this data to the study propositions, figure 7.5 displays that at least one of the theoretical validation themes that relate to study propositions, P1 to P5, have been observed in the field.

Figure 7.6: Semiotic Analysis Summary



7.8.1 Culture and Attitude (project environment)

The case study validation process was encircled by the environmental boundaries of the construction and pharmaceutical organizations.

The validation service provider's background and experience was aligned with that of the construction industry and not the healthcare industries. The client's appointed VSP was unable to successfully provide system process input, in the form of validation protocols, in a consistent and timely manner.

The task environment appeared to be unfamiliar to a number of VSP 2's team; this was observed by reduced system overlap through communications and resource problems. Experience of facility validation in the construction environment was minimal and this hindered process transformation.

The client organization did not appoint sufficient resources to sub-processes, thus reducing process control. Observed monitoring and reporting problems, by the client, were noted in the project environment, partly as a consequence of the different interfacing sub-cultures of the client's project team.

7.8.2 Planning ((time and cost), communication, integration, resource).

The planning process was based on a matrix, showing facility systems, an assessment of criticality and an estimation, from previous experience, of the task duration and associated cost. The schedule was prepared by the client's validation manager and was planned around the commissioning specialists work program. The client stated the validation activity planning should not be undertaken by VSP2, as their skills and understanding did not match those needed to asses the requirements of the installed building systems.

7.8.3 Implementation (control and sequence, change and partnering).

Analysing the time series implementation of the validation process, by utilizing pattern matching, established that there were some deviations from the cybernetic model.

Firstly, the user requirement was produced in line with the literature, however, the other essential pre-qualification document, the functional specification, was not used at any stage in the project. This deviates from the fundamental purposes of pre-qualification activities suggested by the literature review and resultant embedded GMP none conformances (EFF's) were discovered by internal audit, sometime after project completion.

Design review stage was completed retrospectively after project completion. This established a significant difference between the cybernetic model and the analytical data.

IQ and OQ document production was produced at the late stages of the project and was not subject to rigorous approval.

Control procedures were weak and did not ensure that the validation process was complete on handover. Limited understanding of validation methodology and site based problems such as equipment identification, calibration and project documentation flow became major roadblocks to achieving system control.

7.8.4 System Complexity (termination, start-up and commissioning)

Complexity was observed on two levels; Building systems complexity and manufacturing system complexity.

As identified in this study and case study A inadequate testing documentation for some of the building systems was produced. Manufacturing system complexity interfaced in the task environment with the buildings complex HVAC system. Adaptation was low and the task of integrating the two sub-systems in the project environment resulted in a project time delay.

7.8.5 Quality and Regulatory Compliance

Again, major critical omissions were made in the IQ and OQ testing protocols and this indicated limited process knowledge by the VSP. The clients GMP requirements were not clearly expressed and communicated and without a functional specification phase, were not implemented at the facility design stage. Instead during the validation process non-conformances were identified and corrected, which, in the case of the project critical instrument assessment, prolonged the validation activities.

The overall impression of the case study was that the validation service provider was not properly experienced to deal with the complexity of the task environment. In addition control problems may have been avoided if the client organization had been more adaptive at the project interface. The number of subsystem interconnections in the client organization was great and caused operational difficulties.

With respect to the cybernetic model, Case Studies A and B have both demonstrated problematic implementation caused by limited understanding, planning, adaptation and control. To provide further examination of the model and compare emergent categories, pattern matching and to test for replication and structural correspondence, Case Study C is presented in the following chapter, Chapter Eight.

Chapter Eight: Case Study C – Results and Analysis & Discussion of Case Studies A, B & C.

The third of the case studies is presented in-line with the case study methodology outlined in chapter five. This chapter presents qualitative case study evidence in the form of case study C.

Code categorizations that emerged from the orientation and theoretical sampling phases of Case Study A, which are represented by the three level code family tree, were used to code and theoretically sample the third data set derived from Case Study C.

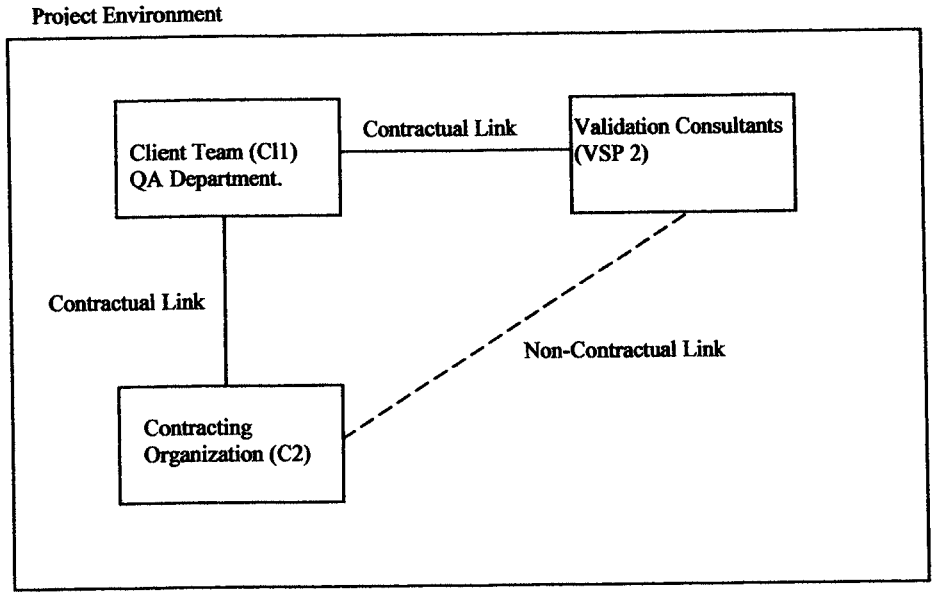
The results for the third case study are presented and analysed followed by a discussion of all case studies.

8.1 Project Description

The project was the construction of a tablet compression facility. The compression facility consisted of a number of manufacturing suites each with materials and personnel airlocks and compression rooms which housed tablet presses. The compression area was constructed adjacent to the sites existing tablet manufacturing facility. This case study focuses on the first two phases of a four phase project. The existing tablet manufacturing department was to be demolished and rebuilt in four phases within the confines of the existing site boundary.

The two phases of the construction project had an initial construction programme duration of nine months (phase 1, June 2002 to November 2002 and phase 2, November 2002 to February 2003). The construction management project had the following structure:-

Figure 8.1 : Case Study C Project Environment



The main groups involved in the study were the client (Cl1), construction management contractor (C2) and the Validation service Provider (VSP2), with assistance from the client QA group.

In line with case studies A and B the following is analysed under the problematic theme headings derived from the literature.

- Culture and attitude (project environment)
- Planning ((time and cost), communication, integration, resource).
- Implementation (control and sequence, change and partnering).
- System Complexity (termination, start-up and commissioning)
- Quality and Regulatory Compliance

8.2 Culture and Attitude - project environment

Validation Service Provider 2

Commissioning and validation of the tablet compression suites was the responsibility of VSP 2. The validation service providers work package included validation of the

compression suites building systems and associated utilities which included HVAC, room monitoring systems and construction of the compression rooms. Again all equipment and process systems were validated in-house by the client. The main organizational difference in this case study project was that the client made available resources to assist in the validation of the compression suites.

Main Contractor 2

The tablet compression suites were constructed by contracting organization C2 who had previous experience of microelectronic clean room manufacturing facilities.

Architect and Building Services Engineering Consultant

Both the project architect and building services engineering consultant were based in the north of England and had substantial experience of pharmaceutical manufacturing construction projects.

8.3 Planning ((time and cost), communication, integration, resource)

A check matrix (C5 and C7) for the compression project fabric and environmental validation was constructed by the client. The check matrix approach tabulated the levels of validation activities required against the new systems that were to be installed. The matrix approach in this case identified that DQ, IQ, and OQ testing was required.

This matrix defined both the level of system validation required and the sequence in which it should occur.

The cost and time schedule for the validation process was produced by the clients QA validation manager. Cost was based on a quotation received from the validation consultant, who calculated his cost on the main contractor's project documentation and past experience of other projects. Scheduling of the various validation tasks was undertaken by the client's QA validation manager based around the commissioning and building work information received from the main contractor and his sub-contractor. The content of the validation protocols produced by the validation consultant was substantially revised following numerous client reviews of this documentation.

System Identification

In this case again only some items of plant and equipment were identified prior to the IQ works which caused confusion for the validation consultant and client. The identification relied on the building services engineer producing amended drawings that the main contractor utilized for ascertaining equipment identification. The final positioning of all component identification tags was the responsibility of the main contractor, who occasionally failed to attach a tag or identify and tag correct plant items. In an attempt to progress the validation works the client considered that rather than waiting for the main contractor and building services engineer to locate and identify the critical system components, the client's validation team proceeded to identify and tag equipment. This allowed items to be included in the installation qualification checks and be calibrated prior to operational qualification tests (C8).

8.4 Implementation (control and sequence, change and partnering)

User Requirement Specification

A User Requirement Specification was written for the site re-development project and approved in October 2001. In line with the recommendations of the literature in Chapter Three a multi-disciplinary team was involved in the production of the document.

Functional Specification

During my fieldwork observation I was unable to ascertain if a functional specification was produced for the tablet compression project. There were no references made to the document by the project team and the likelihood is that a document was not produced.

Validation Master Plan

The Validation Master Plan for the site re-development project was approved in December 2001. Again, a multi-disciplinary team was involved in the production of the document. Representatives of the clients engineering, production, quality

assurance, product transfers and health, safety and environment departments were again signatories in the document approval.

Design Qualification

A design review was not undertaken as part of the validation process for the tablet compression project. The client had however stated in his VMP that:

> prospective validation of plant facilities and equipment begins with Design Qualification....this is a review process which verifies that the supplied design complies with the original requirements (URS, FS, specifications, drawings and approved designs) and GMP.

Installation Qualification

Validation Service Provider 2 produced installation qualification documents for the building systems of the project in March 2003. The testing documentation had only been approved less than two weeks before the pre-planned start of the site works. The installation qualification was executed in March 2003.

Operational Qualification

Validation Service Provider 2 produced operational qualifications for the building systems of the project in March 2003. The documents were signed as approved, by the writer and validation manager (client). None of the user groups or departmental heads provided with the document actually confirmed their approval of the content. The protocol was executed in March and April 2003.

Change Control

A major system deviation, was initially identified by the validation consultant, was that the de-humidification system, that supplied low humidity air to one of the compression manufacturing areas, was not fitted with adequate filtration and monitoring equipment. This omission had been overlooked at the design stage. As previously reported a design qualification, of the HVAC system was not included as part of the validation activities. The deviation was discovered during the installation qualification stage and as a result the building services engineer had to partially re-design and document the changes. An instruction was then given to the main contractor to implement the remedial works.

The changes slowed project progress and resulted in modifications being made to both the IQ and OQ HVAC testing protocols (C14). Validation delays were also caused by incomplete operation and maintenance documentation, inaccurate 'as-fitted' drawings and extra commissioning and calibration works.

8.5 System Complexity (termination, start-up and commissioning)

The integrated HVAC and environmental monitoring systems for the initial phases of the project were not sufficiently commissioned prior to validation. Commissioning tasks at the final stages of the control engineer's contract were not integrated with VSP 2 or the clients QA organization. The level of system complexity was high and inefficient communications between the client and contractor C2 resulted in time delays. These delays occurred only because partial control system commissioning checks were executed. Room pressure monitoring equipment and critical control probes were not configured for the individual production areas (C12). Additional site attendance by the environmental controls commissioning engineers was not established as part of the initial sub-contractor contract and a formal instruction was required from them to proceed with the works.

Project Termination

The majority of the validation works were carried out after the main contractor had handed over the facility. The commission phase of the project was drawing to a close and opportunities for the commissioning and validation teams to work as an integrated team had been lost.

The first phase of the tablet compression project consisted of a hand-over of four completed suites. Due to production constraints and availability of tablet manufacturing presses the occupation of the suites was staggered. The client's validation manager made the decision not to complete the validation of the four suites immediately after hand-over. Instead he awaited notification from the production department of the date each room would be required. Individual validation of the rooms resulted in the process of validation now being retrospective. The majority of commissioning had been completed and other works required on site shifted the focus of attention.

When final testing of the first of the phase one suites was undertaken specific issues, such as room monitoring system equipment and HVAC systems being divided between different areas, had major affects on progress (C16). Validation protocols required modification and drawings that were thought to be 'as constructed' were incorrect and needed modification prior to inclusion into the site validation package records.

8.6 Quality and Regulatory Compliance

An example of embedded non-conformance was demonstrated by the omission of a door as it was considered to have no functional significance in the design of a facility production area.

When discussed on site between *some* of the design team as to whether the door was needed, it was agreed that it could be omitted from the design and considered a cost saving. However, when the HVAC system was commissioned airflow faults occurred in adjoining dependant areas where the door should have been fitted and airflow paths that were critical to achieving room pressure differential could not be set up as one major airflow path. The error was later discovered on a site visit by the HVAC designer and became a fault in the installation.

This resulted in a failure that required extensive remedial works.

Validation Documentation

VSP2's facility validation document package was reviewed by the client (C20) and was found to be inadequate in a number of key areas (C19).

The specific areas where the installation qualification deviates from the recommendations of the literature are as follows:

Installation Qualification

The IQ protocol document included incorrect information relating to critical components or pieces of equipment (C19). One of the main reasons for inaccurate detail was attributed to the document distribution system which did not provide important schedule information to all project parties.

Test procedures were not adequately developed and the acceptance criteria were vague. Regulations or current standards were not generally referenced in the acceptance criteria.

Again, VSP2 demonstrated a lack of GMP understanding by applying a simple 'cut and paste' technique based on other protocols. The production of inaccurate and incomplete documentation lead to a time consuming checking process for the client.

Installation and Operational Qualification

Many of the documentation problems highlighted in the client's review of the IQ protocols were carried over into comments made about the OQ documentation. The fundamentals of installation and operational testing documentation had been missed. The terminology used by the protocol writer was not as expected from a proficient well experienced validation engineer. An unfamiliarity with industry standards, calibration, maintenance and production of protocols emerged from the client's review of the validation service provider's documentation (C19). This is demonstrated by a number of comments made by the client;

> Objective - refers to an IQ document rather than OQ...the "reviewed by" text is only required on the last page of every test section..

Direct and Indirect Classifications

The IQ protocol did not differentiate between critical and non-critical equipment. Items that were critical and of direct impact upon the quality of the product were missed from the protocol. Identification and documentation of critical items became a project task for the clients engineering calibration team (C22).

Building Fabric Installation Qualification

A production area building fabric installation qualification protocol was written by VSP2 and the clients QA department. The document was produced to address those areas of GMP compliance set out in the construction section of the client's user requirement specification. The protocol was produced to test the physical properties of the internal components of the structure based on the clients URS and the architects schedule of finishes and colours.

The document distribution system was such that all revisions to the architect's schedules were not communicated to VSP 2 and the clients QA team. This resulted in re-writing sections of the building fabric IQ when deviations occurred, if the change was discovered before document approval, or noting in the protocols that a deviation had occurred between the expected and actual result of the test. Both outcomes caused downstream repercussions and in the first case, additional time was taken to produce and then approve the protocols. Where a deviation was noted between actual and expected test results, the document executor had to decide on the correct actions to take if indeed any were required. If the deviation was considered minor and did not affect physical performance comments were made in the protocol to this effect. If deviations were more serious corrective actions were required. Where more critical deviations did occur, occasionally opportunities were given to the contractor, by the client, to rectify the deviation prior to the documentation exercise.
This was generally the adopted philosophy for the whole of the validation documentation execution. At times, a number of the validation engineers conducted an almost retrospective approach to the process, where component and equipment details were noted with documentation only serving as a record of what was installed.

8.7 Semiotic Data Analysis

To determine the frequency and importance of emergent themes a project code matrix was constructed from data sources C1 to C25. A semiotic data analysis was then undertaken of the data. The multiple code frequency searches of the data files were conducted using manual techniques. Figure 8.2 shows the project code matrix and figure 8.3 and 8.4 show the semiotic data analysis.

Figure 8.2: Project Code Matrix

Code Family / Data Ref.	Complexity	Contract	Cost	Experience	Implementa	Implmodel	Partnering	Quality	Termination	Time	Validation
C1.	X	X	X	X	X	X	X	40,40,41, 42	X	X	X
C2.	X	X	X	X	X	X	X	41	X	X	82
C3.	X	X	X	X	X	X	X	41	46	X	X
C4.	X	X	X	X	30	X	X	X	X	X	73
C5.	X	X	X	19	29	X	X	X	X	60	63
C6.	X	X	X	X	X	X	X	41	X	X	83,87
C7.	X	X	X	X	X	X	X	40	X	X	63
C8.	X	X	X	X	21	X	X	X	X	52	X
C9.	X	X	18	X	26	32	X	X	X	X	X
C10.	X	X	X	X	X	X	X	X	X	X	87
C11.	X	X	X	X	X	X	X	X	X	49	X
C12.	05	07	X	X	21,22	X	X	X	48	55	87
C13.	05	X	X	X	X	X	X	X	X	X	73
C14.	03	X	X	X	X	X	X	X	X	57	63,67,87,88
C15.	X	X	X	X	X	X	X	X	X	X	87

Figure 8.2 (Continued): Project Code Matrix

Code Family / Data Ref.	Complexity	Contract	Cost	Experience	Implementa	Implmodel	Partnering	Quality	Termination	Time	Validation
C16.	03	X	X	X	X	X	X	X	X	X	X
C17.	X	X	X	X	X	X	X	X	X	X	87
C18.	X	X	X	X	X	X	X	X	X	X	87
C19.	X	X	X	X	X	X	X	X	X	X	73,76
C20.	X	X	X	X	X	X	X	X	X	X	73,76
C21.	X	X	X	X	21,21,21	X	X	X	X	X	X
C22.	X	X	X	X	27	X	X	X	48	X	X
C23.	X	X	X	X	X	X	X	X	X	X	63,67,70
C24.	03	X	X	X	X	X	X	X	X	X	X
C25.	X	X	X	X	26	X	X	X	X	X	86

8.8 Discussion

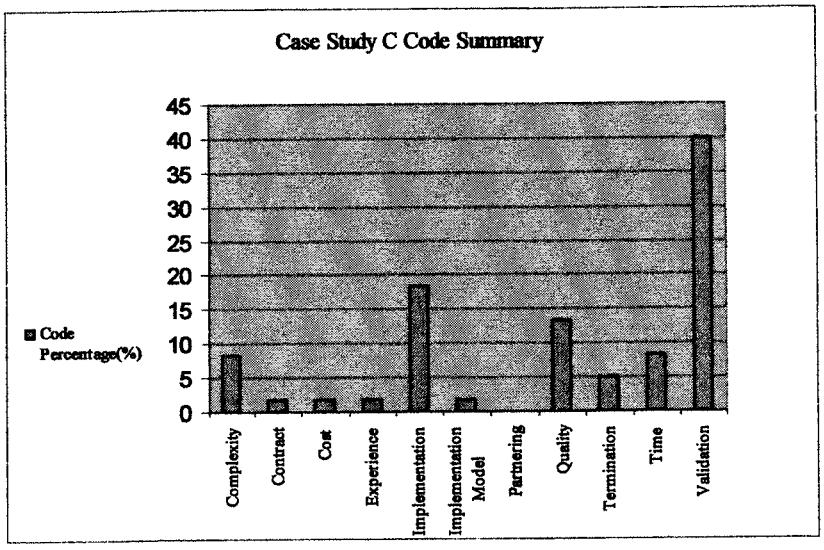
Categories that emerged from the case study data set are tabulated below in figure 8.3 and displayed in figure 8.4.

Figure 8.3: Case Study C – Semiotic Analysis Summary for data C1 to C25

Code Group	Code Frequency	Code Percentage
Complexity	5	8.3
Contract	1	1.66
Cost	1	1.66
Experience	1	1.66
Implementation	11	18.33
Implementation Model	1	1.66
Partnering	0	0
Quality	8	13.33
Termination	3	5
Time	5	8.33
Validation	24	40

With reference to figures 8.3 and 8.4, the data presented shows an emergence of a number of particular important themes which relate to the study propositions. Observations with the highest frequency counts were in the implementation (18.33%), validation (new emergent code) (40.0%), quality (13.33%) and time (8.33%) categories. Relating this data to the study propositions, figure 8.4 displays that at least one of the theoretical validation themes that relate to study propositions, P1 to P5, have been observed in the field.

Figure 8.4: Semiotic Analysis Summary



8.8.1 Culture and Attitude (project environment)

The case study validation process was encircled by the environmental boundaries of the construction and pharmaceutical organizations.

The validation service provider's background and experience was aligned with that of the construction industry and not the healthcare industries. During the case the building services project group reduced its input into the project environment. This appeared to be related to their dissatisfaction with the clients continued requests for validation assistance in the form of documentation modifications, such as revisions of 'as fitted' drawings to accommodate project change. The site-development contract was drawing to a close and commitment and effort was starting to diminish.

The other marked difference between case A and the other cases was that the project termination phase was prolonged because the start-up requirements for project sub-systems were staggered. Validation of each facility sub-system became a retrospective process which caused a series of specific problems.

Other marked changes were that the clients project input increased in the form of resource. This boundary shift emerged from a growing dissatisfaction with the limited level of expertise provided by validation consultants.

8.8.2 Planning ((time and cost), communication, integration, resource)

The planning process was again based on a check matrix which showed facility systems, sequence and level of validation coverage. The planning activity was completed by the client as he considered that the VSP had insufficient skills to accurately estimate project durations.

8.8.3 Implementation (control and sequence, change and partnering)

Analysing the time series implementation of the validation process, by again utilizing pattern matching, established that there were some deviations from the cybernetic model.

Firstly, a user requirement was produced, however, the other essential pre-qualification document, the functional specification, was not used at any stage in the project. This deviates from the fundamental purposes of pre-qualification activities. The

design review stage of the project was omitted and IQ and OQ document production was produced at the late stages of the project and was not subject to rigorous approval.

As the client did not require use of all of the tablet compression suites the validation activity was not fully executed immediately after handover from the main contractor. This resulted in a retrospective validation approach being adopted and subsequent excessive re-commissioning when each new suite was required for production.

Site based problems such as equipment identification, calibration and project documentation flow were seen as major roadblocks to achieving system control.

8.8.4 System Complexity (termination, start-up and commissioning)

As in case studies A and B, this study identified inadequate testing documentation for some of the building systems. Manufacturing system complexity interfaced in the task environment with the buildings complex HVAC system. System positive feedback, which amplifies error, occurred in the project up until a critical point where the client reviewed the production suite HVAC system operation. The system was unable to adequately control the room GMP parameters such as differential pressure and it was concluded that remedial actions were required. The actions taken consisted of costly system modifications, re-commissioning and re-validation. Control complexity was such that the environmental controls commissioning engineers and the validation team spent a large amount of time 're-learning' system operation.

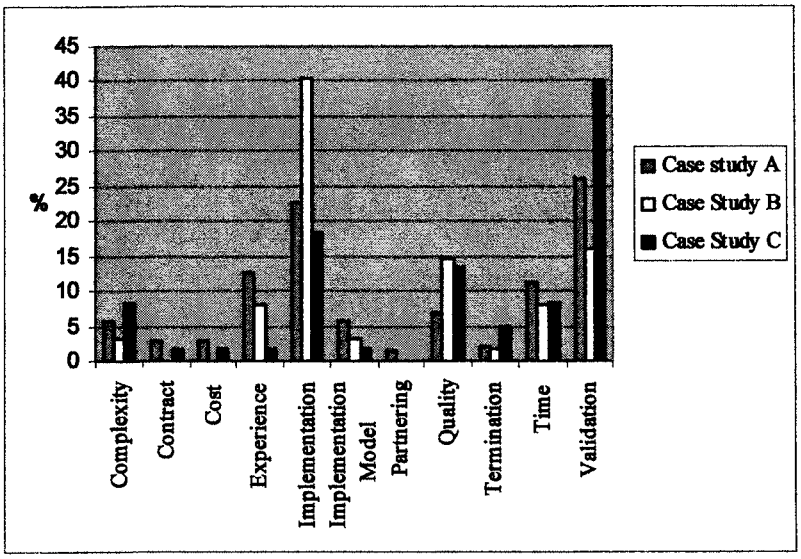
8.8.5 Quality and Regulatory Compliance

Again, major critical omissions were made in the IQ and OQ testing protocols and this indicated limited process knowledge of the VSP. The criticality of system instrumentation was not identified at an early project stage and the responsibility became that of the client's organization. Common problems were observed which indicated a lack of understanding of the validation service provider. Control problems were caused by the retrospective approach which caused costly control 'lag'.

8.9 Discussion of Case Studies A, B & C

The propositions presented in chapter four, have been assessed by observing, collecting and analyzing data from three case studies. By using semiotic analysis, as described earlier in chapter five, it was possible to identify six distinct themes. These themes (*complexity, experience, implementation, quality, time* and *validation*) are shown in figure 8.5 below.

Figure 8.5: Summary of Semiotic Analysis



The themes were further analyzed into a number of sub themes (from the coding process). Figure 8.5 represents the occurrence of the themes as a percentage of the total number observed.

Figure 8.6: Summary of Case Study Codes.

Code	Case A (%)	Case B (%)	Case C (%)
Complexity	5.60	3.20	8.30
Contract	2.8	0.0	1.66
Cost	2.8	0.0	1.66
Experience	12.67	8.0	1.66
Implementation	22.53	40.30	18.33
Implementation model	5.60	3.20	1.66
Partnering	1.40	0.0	0.0
Quality	7.0	14.51	13.33
Termination	2.11	1.60	5.0
Time	11.26	8.0	8.33
Validation	26.05	16.12	40.0
	100%	100%	100%

SPSS correlations were computed for the emergent themes and this showed a strong correlation between cases A and B ($r = 0.798$, $p = 0.003$) and cases A and C ($r = 0.845$, $p = 0.001$). A weaker and less significant correlation was calculated between cases B and C. See Figure 8.7.

Figure 8.7: Case Study Correlations

		Case A	Case B	Case C
Case A	Pearson Correlation	1	.798(**)	.845(**)
	Sig. (2-tailed)	.	.003	.001
	N	11	11	11
Case B	Pearson Correlation	.798(**)	1	.595
	Sig. (2-tailed)	.003	.	.054
	N	11	11	11
Case C	Pearson Correlation	.845(**)	.595	1
	Sig. (2-tailed)	.001	.054	.
	N	11	11	11

** Correlation is significant at the 0.01 level (2-tailed).

By the process known as methodological triangulation (Patton, 1987, p.60) the propositions that were suggested at the outset of the study were found to be supported by the fieldwork.

8.9.1 Pre-Qualification Activities: User Requirement and Functional Specification

With reference to Figure 8.8, the first requirement of the pre-qualification activities and arguably the most crucial is the specification of the requirements of the building user.

Figure 8.8: Case Study Pattern Matching –Activity Sequence

	URS	FS	VMP	DQ	IQ	OQ
Case A	Yes	Yes[1]	No	No[2]	Yes	Yes
Case B	Yes	No	Yes	Yes[1]	Yes	Yes
Case C	Yes	No	Yes	No	Yes	Yes

1 - Produced post project, 2 – Phase not completed.

A URS was produced in each of the cases (See Figure 8.8 above) and there were differences in content and documentation procedures varied, which affected application.

In case study A the URS was produced by the validation service provider and contractor and was noted by the client validation manager as not providing any confidence that the document was of a sufficient regulatory level. The document approval was limited to a single discipline reviewer, undermining the multi-discipline approach suggested in chapter three.

Case studies B and C both used a user specification produced by the client's project teams. The specification deviated from recommendations outlined in chapter three in relation to specifying critical systems and testing procedures. The documentation did not provided specific information with regards to the validation of building systems in terms of building fabric and environmental requirements.

In case study projects B and C there was no use of specifications as a way of assessing the design solution against user requirements and project A only addressed this issue at the final stage of the project.

8.9.2 Validation Master Plan

Project A did not utilize a validation master plan and the four main reasons for application have been examined in section three and were:-

1. To allow validation to be built into the project environment and make team members aware of the requirements.
2. To allow the project manager to keep track on progress.
3. To give a measure of completeness of the validation side of the project.
4. The plan will give auditors or regulatory agencies an understanding of the company's approach to validation and the set up and organization competence of all validation and project activities.

Project A suffered from communications difficulties between groups and unclear project quality requirements which may have been caused by limited client involvement at the user requirement stage. Without well defined requirements the design and build group were not able to provide a building that was based on a wide range of specialist knowledge. Cases A and B had validation master plans produced which addressed the correct areas of implementation .With reference to the key VMP uses identified above as points one to four ~~above~~, the planning stage helped to make other disciplines aware of validation, most team members were already aware of the validation process. The ability of the validation manager to measure construction progress was limited by his understanding of this environment which effected integration of the project termination phases. The planning documentation did not allow a detailed assessment of validation progress as modifications to project schedules were not included as document revision history.

8.9.3 Design Qualification

In all case studies it was the design qualification or review stage that was least well implemented. The main reason may be that early regulatory requirements such as those published by the MCA/MHRA did not expressly call for design audits. The

situation has changed with the EU directives indicating use of DQ procedures. It appears this regulatory deviation has caused industry confusion and accounts for the omission of the stage process. The post project sequence of implementation in case B made little sense as it would not be possible to correct the deviations highlighted by the DQ prior to installation and IQ and OQ testing phases.

The pre-qualification activities of URS, FS and DQ have been observed as having a major impact on the subsequent downstream validation stages and final project outcome.

8.9.4 Installation and Operational Qualification

8.9.4.1 Static and Dynamic Testing

Roper, (1994) notes that testing, be it of computer software or any system or sub-system, can be classified as static or dynamic. Static techniques are those that examine a system and include the activities of inspection, symbolic execution and verification. Dynamic testing relates to techniques of generating test data for execution by the software or system.

Validation techniques also follow the same pattern of static and dynamic testing where the design and installation tests consist of examination, comparison and verification of the system and are static in nature. Operational qualification tests are generally dynamic and are normally utilized to check the facility across its operational range.

A common problematic pattern that emerged from all of the studies involved incomplete system inputs in the form of field plant identification and project documentation. Static testing techniques employed in installation verification require system reference data to allow visual inspection, feedback, comparison and control action. The planning stage of the project failed to identify group responsibilities which resulted in unidentified tagged building systems and documentation that prohibited adequate static testing. This resulted in delay and conflict between project team members.

All of the case study projects demonstrated that validation documentation and implementation was deficient in common areas. These were:-

1. Testing strategy.
2. Maintenance schedules.
3. Critical systems identification. System risk analysis.
4. Acceptance criteria.
5. Calibration requirements related to (3).

System testing can be classified as black box or functional testing and structural or white box testing. Black box techniques refer to test cases that deal without construction of the transformation process and rely on specification or description of what the system should do. The transformation process is treated as a black box and its function is tested by applying different input stimuli. Case study projects demonstrated that the validation test strategy resembled partly that of 'black box' testing where only functions or system outputs were analysed. This was displayed in case B where space temperature and humidity mapping tests measured the output of the HVAC system only on a given day. Operational tests prior to this did not in fact demonstrate that over a wider range of test stimuli i.e. high ambient humidity, the system could achieve desired output in line with the URS.

Black box testing suffers from the drawback that it focuses on the output relationship with the specification and not on the actual transformation. As a result, the amount of system actually being tested is unknown and testing omissions are possible. There may be something present in the output that does not meet the specification and the system performs some undesirable task that the black box inputs have not detected. White box testing is the exact opposite of the black box technique, where test cases are derived by examination of the construction of transformation process.
A combination of both structural and functional testing procedures would appear to be desirable.

8.9.5 Experience and Attitudes

Validation team members come from a variety of professional backgrounds. Experience of a significant number of the validation teams in the case studies was initially gained from scientific backgrounds relating to either chemistry or biology which affected their ability to validate building systems. All of the validation service providers relied greatly on the client's quality assurance team to assist. The design and build contracting organization (C1) displayed a greater level of understanding and appreciation of client GMP requirements. Experience of contractor (C2) was wide reaching but general, which limited his ability to integrate in the project environment.

The interviews indicated that within the task environment there were two different and opposing goals. The primary concern of the pharmaceutical client was the integration of manufacturing technology and production start-up whilst the contracting organization's focus was mainly the provision of the building and associated services. These opposing goals and industry views contributed to a reduction in system adaptation. Groups enter the task environment with predefined cognitive attitudes and goals. The pharmaceutical organization's primary concern is the manufacturing process and the building is of secondary interest. In case study A the pharmaceutical validation manager referred to the facility as an 'enclosure', this view appeared to be simplifying the facilities basic functional purpose.
The construction project manager (C1) was unaware of the quality requirements of the project and worked only to the contract documentation. The project specification had been produced by the Validation Service Provider and was not communicated to other project groups. The design and build contractor's primary focus was most definitely the construction process.

8.9.6 Planning – Time and Cost

The most common methods noted in the case studies for calculating validation costs were in line with those suggested by the literature, i.e. by a planning matrix based on

previous experience of the process. Fieldwork data, obtained from case studies A and B, also showed that 'check matrix' systems were utilized in planning.

A common problem recognized across all cases was the limited ability of the Validation Service Provider to identify specifically 'which' systems and 'how much' testing was required. This inability to plan the validation activity resulted in very inaccurate project schedules.

8.9.7 Complexity

The complexity of the validation process was demonstrated in case study B[1] where project data collection and control procedures were highlighted by the pharmaceutical organization as being major problematic factors in controlling the project.

In case study project A the level of validation documentation was not able to adequately address, by testing, those system functions and attributes that were considered by the client as critical. The complexity of a number of the building systems was such that the Validation Service Provider was unable to generate suitable test procedures due to his lack of system understanding. *Building system complexity* also impacted on the building owner's maintenance personnel who struggled with the high technological complexity of the HVAC and monitoring systems. Project A was primarily a pilot project, to asses the suitability of new manufacturing technology systems. *Process system complexity* in case A was considered high and integration between the facility and the 'built in' plant was problematic and caused project delay. The complexity issues of new technologies were noted by contractor (C1) as 'having repercussions that have to be taken into account'.

8.9.8 Partnering

Although partnering was not the unit of analysis for the study and was not fully explored, the organizational relationships within the project environment were examined. In case A a partnering arrangement existed between the main contractor

[1] See section 7.5, Case Study B.

and the commissioning organization. This relationship benefited the validation process as the close working relationships between contractor and commissioning engineer which provided accurate and clear operation and maintenance documentation which was used in the documentation process.

8.9.9 Implementation – Control and Sequence

Variations in design have a direct affect on the validation cost and schedule. Changes made are often not reflected in the validation testing protocols. Pharmaceutical facility projects require that the project team can recognise, assess and document change. A number of significant changes occurred in the case study projects caused by poor information exchange between the client and main contractor.

The number of significant changes that occurred may have been avoided if a design review had been carried out by the project team, at the correct stage in the projects. The system control procedures varied in their ability to control the validation activity. Control in project A was weak because sub-process output sensing and feedback was not well defined, or in the case of the DQ sub-process, did not occur in the correct time series manner.
In case B the DQ sub-process was omitted and this permitted conformance deviations to progress to the IQ sub-process. The consequence of the embedded non-conformance not being identified and rectified at an early stage resulted in additional cost and delays because of the required remedial works. The importance of early stage quality checks at the URS, FS or DQ stage or collectively termed pre-qualification (Pre-Q) are critical in reducing major design deviations occurring post construction.

Common control deficiencies that effected system output were observed between the case study construction projects:-

1. The system transformation process was validated as a 'black box' system. This was demonstrated by the large number of functional tests in the validation protocols. In some cases structural testing was ignored or considered of secondary importance.

2. System goal states were undefined and contained embedded none compliance. This was exhibited by vague acceptance criteria in testing protocols.

3. The process output deviation from the goal was so large between events that 'swing' or 'lag' was observed. Lag is a swing away from the goal prior to feedback correction and requires a more forceful reaction to attain control.

4. Too few inputs permitted sub-systems to become 'closed'.

5. As suggested by Warboys et al (1999), the limited degree to which adaptation took place is related to the ability to respond to environmental stimuli. The level of adaptation is reliant on the organizations having stimuli that they have the structure to recognise.

8.10 Quality – Critical Systems and Regulatory Compliance

All case study projects demonstrated that those implementing validation commonly fail to identify and document direct and indirect systems and sub-systems in accordance with the literature recommendations of the ISPE.

Regulatory requirements and identification of those systems and components which may impact on the quality of the manufactured product appear to be inadequately understood.

The process of constructing and validating a pharmaceutical manufacturing facility occurs through the construction and pharmaceutical environments overlapping to form a new project or task environment for the duration of the project. The study has highlighted that there are cultural differences between the two project groups and that the location of the regulatory information pool is in the domain of the pharmaceutical sector. The term regulatory information pool can be said to contain knowledge from a wide variety of sources such as individual's knowledge, regulations, industry journals, conference papers and audit and inspection data. Communication and integration between the construction industry and the pharmaceutical client is therefore critical to permit this knowledge to be placed into the project environment.

8.10.1 Project Termination

Meredith & Mantel, (1989) have identified that the project termination phase has one of three outcomes i.e. extinction, inclusion and integration.

Case study projects A and C terminated by extinction where the project simply stopped and was perceived by *some* of the project group to have been successful and achieved its goals. The pharmaceutical project group viewed the projects as only partially successful.

Project B terminated in a way that partly represented integration, where input from the main contractor in the form of instruction and advice increased the client's knowledge of the facilities operation and maintenance. The project integrated handover procedure also assists the validation effort as project record documentation is provided earlier than would be the case in projects that terminate by extinction.

In all cases the majority of validation activities took place in the termination phase and it was observed that great stress was put on project budgets or scheduled time available.

There was also clear evidence that the priorities of contractor and client differed and in case study A the commissioning activity was carried out in isolation from the facility validation, this is at odds with the integrated approach suggested by Dream & Jester (1997).

As noted earlier the construction and validation of pharmaceutical facilities is undertaken in an overlapping environment which contains two different cultures. On completion of the facility the project environment overlap retracts and the parent environments separate and the building returns to the pharmaceutical environment. The validation of the facility will be scrutinized and its ultimate success will be determined by agency regulators. The study data indicates that the quality of the finished building will be very much aligned with the pharmaceutical meaning and not the construction view of build quality. The research has also underlined that project success measured by the building owner is dependant on the implementation and control of the validation process. In a situation where two groups exist with different project priorities there is a need for increased integration and adaptation within the task environment.

The final part of the empirical study, an industry survey is presented in the following chapter, Chapter Nine. The industry survey uses a questionnaire as the data collection instrument and is included as an additional analytic phase to the study. It provides external validation to the case study element of the research to further inform the cybernetic model.

Chapter Nine presents an initial discussion of the use of questionnaires and their design in the context of this research and presents the results and analysis of the survey.

Chapter Nine: Survey Questionnaire– Results and Analysis

9.1 Introduction

An industry survey was undertaken to provide external validation to the study propositions and model that emerged from the literature review and case study analysis. The industrial survey took the form of a postal questionnaire as the data collection instrument.

The case study data has provided in-depth information and perspectives of a relatively small number of respondents. Gray (2004, p.187), notes that supplementary data may also be gathered from a wide-scale survey to follow up the interviews and observation data. Such commentators suggest that research involving case studies commonly use a combination of data gathering methods including questionnaires. Howe & Lewis (1993, p.58) support this suggestion and comment that the survey questionnaire forms the basis or a contributing part of a large number of research projects. Questionnaires are a very common method of social research (Bechhofer & Paterson, 2000, p.72) and have been used in construction research together with case study methods by Griffith & Headley (1995). Successful application of questionnaires have been reported in the construction industry press by writers such as Akintoye (2000), Zarkada-Fraser & Skitmore (2000), Lam *et al* (2001) and Low & Tan (2002).

The popularity of questionnaires is discussed by Gray (2004, p.188) and Bechhofer & Paterson (2000, p.72) and it is argued that a highly structured questionnaire is both low in cost and time demands. As opposed to interviews the respondent can complete the questionnaire at his or her convenience and is not required to meet the researcher, thereby assuring anonymity.
In addition, structured questionnaires do not suffer from interviewer bias where emphasis may be placed on certain questions. Successful formats employ standard, easily understood questions which should not be open to individual interpretation. Well crafted design will also increase the efficiency of data analysis by including closed, short, easily coded questions.

Questionnaire Objectives

The questionnaire is a method of obtaining information from informants who are asked to respond to a set of questions which are set out in a predetermined order. In this research the answers from the questionnaire form the basis of the fourth dataset as outlined in the data collection model in section five[1].

The main objectives of employing such a research tool are, as noted by Denscombe (1998, p.89), to provide *factual* and *opinion* information. In the case of this study factual information relates to respondents details, such as job title and opinion information in respect to their attitudes and views.

To construct a questionnaire that is suitable for the intended purpose, Baker (1999, p.201) suggests that;

1. The questionnaire obtains as precisely as possible the information that the researcher wants.
2. Is clearly understood by all respondents to mean the same thing, and
3. Is pleasing enough to the respondents that they are willing to spend time to complete it and it is sufficiently engaging that they will not give superficial or misleading answers.

To meet these objectives careful consideration has to be given to the design of the questionnaire, sample selection, piloting and administration.

Sampling

Selection of a sample is based on its representativeness of the population and the fact that the 'samples main characteristics are similar or identical to those of the population' Gray (2004, p.83). The probability method of randomized sampling is employed in this study as it is more likely to be representative than purposive sampling (Babbie, 1998, p.194).

As Baker (1999, p.204) suggests the most important consideration in deciding which respondents to survey is to decide which sets of respondents will be able to answer the type of questions that will be included in the survey. The decision on selection of

[1] See section 5, Figure 5.3.

the appropriate population is based on acknowledging those who have the greatest influence and involvement on the process of validation. The sample drawn from the population therefore includes both the client (Pharmaceutical) and service provider (Construction) groups.

The sample for this questionnaire was based on selecting a cross-section of UK pharmaceutical companies and construction companies who have had involvement with building pharmaceutical facilities. Although the postal questionnaire response rate of 34 out of 75 returned questionnaires was low, the percentage of completed questionnaires (45%) was in line with other construction management research studies (See, for example, Akintoye (2000)).

Administration

The next stage of the questionnaire process and the one that seeks to maximize the questionnaire return rate is administration. Baker (1999, p.204) notes that questionnaires can be either administered to a group, a mail survey, face-to-face, or by telephone. Gray (2004, p.204) also suggests the use of on-line questionnaires as either Web or e-mail formats.

A postal questionnaire was adopted for this study as it provided a considerable amount of data at a relatively low cost and within the minimum of time. Denscombe (1998, p.105) acknowledges the time and cost benefits of postal questionnaires over face-to face and telephone methods. Whilst group administration also has benefits of providing large amounts of data it was not a viable option due to the scattered geographical location of those respondents in the sample.

Although a Web based questionnaire offers many facilities that are not available in paper-based questionnaires it was considered that the extra time to design the questionnaire would not be beneficial. E-mail formats were also rejected as it was considered that the busy practitioner presented with a large amount of daily e-mails may not respond favorably to additional communications of this type.

Piloting

Prior to distributing the postal questionnaire a pilot was developed and tested. Social surveys require to be piloted and as Oppenheim (1992, p.47) points out should be;

> created or adapted, fashioned and developed to maturity after many abortive test flights...every aspect of a survey has to be tried out beforehand to make sure that it works as intended.

Gray (2004, p.205) recommends the use of piloting to reduce the occurrence of non-response and suggests that the following points should be considered when piloting a questionnaire:

1. Instructions given to respondents.
2. Style and wording of any accompanying letter.
3. Content of face sheet data i.e. respondents name and address.
4. Formality or informality of the questionnaire in terms of tone, presentation etc.
5. Length of the questionnaire – if too long, is the response rate likely to be reduced?
6. Sequence of questions.
7. Quality of individual questions in terms of whether they are understood and answered in a way that was intended.
8. Scales and question format used, e.g. Likert scales, Yes/No responses etc.

In line with the above recommendations a pilot questionnaire was constructed to highlight any problems with the wording and structure of the questions. The questionnaire was initially sent to ten people at companies whom it was believed would respond to the questions within a reasonably short period of time so as to expedite the data collection phase of the research. This allowed the recommendations and general problems relating to the questions set to be rectified reasonably early in the study period. The pilot process also gave the opportunity to discuss the content of the questionnaire with a number of project managers. Based on the feedback provided from the pilot the questionnaire was modified by increasing its length and rewording some of the questions so that they related more directly to the study propositions.

9.2 Questionnaire Design

In designing questionnaires the researcher must attempt to, as Gray (2004, p.188) stresses, 'capture the values, perceptions and interests of the respondent'.

The final version of the questionnaire was design so to avoid those questions that Arksey & Knight (1999) suggest may be problematic, such as prejudicial language, imprecision, leading, double, assumptive or hypothetical questions.

The opening questions were designed as *classification or factual* questions. This type of question provides the basis for the analysis giving the responents job title and experience within his or her industry and involvment with pharmaceutical validation.

The remainder of the questionnaire consited of *content* questions which were close rather than open.

Open questions have the disadvantage that they have no pre-defined response and therefore in the context of this section of the study are difficult and time consuming to analyse and compare. Closed questions have pre-defined responses and are easier to analyse.

The final questionnaire provided simple instructions and a clear consistent format. Questions were numbered and grouped into similar subject areas to make them easier to complete and analyse at a later date.

Questions were designed to be relativly short and easily answered from the respondents memory. The use of open ended questions was avoided to ensure that the data could be easily collected and analysed.

The questionnaire was sub-divided into two sections, the first section consisting of specific statements relating to categories from the review of literature and from the grounded theory case study research. The second section of the questionaire was constructed of thirty five propositions relating to the measurement of the respondents attitude of both the construction and pharmaceutical industries.

The study, so far, of the two distinct industry environments has identified that there are are cultural differences in the way in which quality assurance is implemented in each sector. The attitudes or views of pharmaceutical and construction industry practitioners was measured using an attitude measurement scale. According to Blalock (1968) attitude is the stand that people take on an issue. Attitude phenomena tend to be cognitive, behavioral and affective. Cognitive attitude refers to an individual's information regarding an issue. Behavioral attitude is the specific acts a

individual's information regarding an issue. Behavioral attitude is the specific acts a person performs or advocates with regards to an issue and affective attitude refers to an individual's degree of faviourability or unfaviourability towards an object.

The questionnaire (see Appendix C) was sent to two distinct groups within the industry, pharmaceutical validation service providers and construction contractors. Seventy five questionnaires were forwarded and the response received was 45% (34 questionnaires). A response rate of thirty percent is considered typical.

9.3 Rating Measurement Scales

Rating scales are used to evaluate procedures, products, personal or social development and attitudes as well as perceptions and images (Blum and Foos, 1986). The empirical basis for attitude scale construction is likely to consist of the respondent indicating to the investigator what he believes, feels or would do about an object.

The four main standardized methods suggested by Oppenheim (1992) are:

a) Likert scales are scored by summing the ratings given. The participant notes his/her level of agreement/disagreement with a number of statements by ticking the appropriate box. Scales typically have five to seven categories so a neutral response is the mid point, which indicates no opinion. Likert scales provide ordinal measurement of attitude.

b) Thurstone scales or affective/subject scales have equal appearing intervals. Participants are given a large number of statements concerning a subject. The statements are then sorted into a specific number of piles (7 or 11) so that adjacent piles are separated by the same, subjectively determined, interval. After the statements are sorted a median mean value can be calculated to give an overall scale with equal appearing intervals. Scores from such a large scale can then be treated as interval data.

c) Guttman Scales use cumulative ratings and items are arranged so that participants who respond favourably to a particular item are likely to respond favourably to all the remaining items of lower rank.

d) Osgood's Semantic Differential Scale involves rating a procedure, event (etc) on a number of seven point scales. Each scale is anchored by a pair of bipolar adjectives i.e. good / bad, fast/ slow etc. The scale was originally intended to measure the connotative (imply in addition to the primary meaning) meanings of words.

A Likert scale was considered the most suitable measurement instrument for the questionnaire and a five point category scale was constructed . The scale construction involved breaking down the questions into groupings of specific statements which related directly to a proposition areas see Figure 9.1
The decision to send the survey to the two groups was influenced by the model constructed and described in Chapter Four (i.e those who have a direct involvement with pharmaceutical construction projects and those who manage quality,time, costs and resources). The information gained from those involved in this area is significant because it supports the data collected in the literature review and case study field-work and helped in formulating conclusions relating to the study propositions. Client and service provider groups were chosen to give a balanced view of both sides of the validation process. The survey respodents were chosen so as to included the main groups and disciplines who are involved in the process.

Figure 9.1 shows the main problematic categories of focus.

Figure 9.1: Measurement Category Groupings

Category	Measurement proposition
Experience	a) Years involved in construction or pharmaceutical industries. b) Years involved in the validation of pharmaceutical facilities.
Complexity	Q2.2. Validation is complex to implement.
Timing	Q1. The design/construction team are rarely involved with the clients QA team early in the project. Q11.0.Validation normally starts at the initial design stages of a facility Project. Q13.0. The timing of the implementation is crucial to the success of the whole construction project.
Partnering	Q21.0. Projects run more smoothly when an integrated/partnering approach is adopted. i.e. all those involved with any aspect of the project have an input into the project, including validation at an early stage.
Implementation (sequence & control)	Q3.0. Facility validation duration is difficult to estimate. Q3.1. Facility validation duration adds to overall project duration. Q12.0 Validation normally starts when all construction activities are complete as to allow the installation work to proceed without interruption. Q17.0. Validation is generally better left to the organizations who design/install as they have a more detailed understanding of the systems. Q24.0. During the facility validation there are usually sufficient systems in place to allow feedback and corrective action if something has been incorrectly designed, installed or commissioned.
Cost	Q2.3. Validation is expensive to implement. Q4.0. Facility validation cost is difficult to estimate. Q4.1. Facility validation cost is difficult to control. Q5.0. The calculation of facility validation cost is based on past experience. Q5.1. The calculation of facility validation cost is based on planning matrix. Q5.2. The calculation of facility validation cost is based on specialist sub-contractors quotation. Q5.3. The calculation of facility validation cost is based on the time slot available for commissioning at the end of the project. Q6.0. As a percentage of overall facility construction, validation costs are below 5%. Q6.1. As a percentage of overall facility construction, validation costs are between 5% and 10%. Q6.2. As a percentage of overall facility construction, validation costs are between 10% and 15%. Q6.3. As a percentage of overall facility construction, validation costs are between 15% and 20 %. Q6.4. As a percentage of overall facility construction, validation costs are above 20%.

Figure 9.1: Measurement Category Groupings (Continued)

Quality	Q2.0 Validation is only required if the pharmaceutical client asks for it. Q2.1.Validation is an essential requirement for regulatory compliance. Q7.0 Which areas of a pharmaceutical manufacturing site require validation – offices. Q7.1 Which areas of a pharmaceutical manufacturing site require validation – site restaurants. Q7.2 Which areas of a pharmaceutical manufacturing site require validation – product manufacturing areas. Q7.3 Which areas of a pharmaceutical manufacturing site require validation – product packaging areas. Q7.4 Which areas of a pharmaceutical manufacturing site require validation – general circulatory spaces. Q7.5 Which areas of a pharmaceutical manufacturing site require validation – dispensaries. Q7.6 Which areas of a pharmaceutical manufacturing site require validation – warehouses. Q8.0. With reference to production/packaging product contact areas which of the following require validation – Facility internal construction materials. Q8.1. With reference to production/packaging product contact areas which of the following require validation – HVAC systems. Q8.2. With reference to production/packaging product contact areas which of the following require validation – room monitoring systems. Q8.3. With reference to production/packaging product contact areas which of the following require validation – purified water systems. Q8.4. With reference to production/packaging product contact areas which of the following require validation – general indirect utility systems. Q8.5. With reference to production/packaging product contact areas which of the following require validation – product contact gases. Q9.0. Regulations governing the validation of pharmaceutical facilities are too stringent. Q9.1. Regulations governing the validation of pharmaceutical facilities are difficult to understand. Q9.2. Regulations governing the validation of pharmaceutical facilities are too general and not detailed enough. Q9.3. Regulations governing the validation of pharmaceutical facilities are vastly different from country to country. Q9.4. Regulations governing the validation of pharmaceutical facilities are difficult to obtain. Q10.0. A validated facility is considered compliant when it fulfils the requirements of the initial design. Q10.1. A validated facility is considered compliant when it is completed on time and at no additional cost. Q10.2. A validated facility is considered compliant when it satisfies the client. Q10.3. A validated facility is considered compliant when it satisfies regulatory inspection. Q14.0. Project validation should not be necessary if high quality commissioning is carried out. Q15.0. A well written commissioning document could be used in lieu of a validation document. Q20.0. Commissioning should be used to qualify non-critical systems as it is likely that good engineering practice will ensure a properly installed plant or system. Q22.0. Validation is a new area of quality assurance that does not have clear industry guidelines. Q23.0. Validation of a facility is worthless unless a system of continued maintenance is in place to ensure that performance levels are within specification.

Figure 9.1: Measurement Category Groupings (Continued).

Culture and Attitudes	Q16.0. Facility validation should be left to the pharmaceutical client. Q18.0. Most construction companies are not sufficiently experienced to complete the validation of a facility i.e. writing protocols, carrying out tests and reporting outcomes. Q19.0. If an installer is testing a system during installation it is wasteful to repeat the tests as part of a validation exercise. Q25.0. The PHARMACEUTICAL INDUSTRY is flexible. Q26.0. The PHARMACEUTICAL INDUSTRY is profit focused. Q27.0. The PHARMACEUTICAL INDUSTRY is contractual. Q28.0. The PHARMACEUTICAL INDUSTRY is insular. Q29.0. The PHARMACEUTICAL INDUSTRY is efficient. Q30.0. The PHARMACEUTICAL INDUSTRY is research lead. Q31.0. The PHARMACEUTICAL INDUSTRY is highly regulated. Q32.0. The PHARMACEUTICAL INDUSTRY is adequately resourced. Q33.0. The PHARMACEUTICAL INDUSTRY is proactive Q34.0. The PHARMACEUTICAL INDUSTRY is highly technological. Q35.0. Those employed in the PHARMACEUTICAL INDUSTRY Have low job related stress. Q36.0. Those employed in the PHARMACEUTICAL INDUSTRY have high job satisfaction. Q37.0. Those employed in the PHARMACEUTICAL INDUSTRY Receive good pay/employment packages. Q38.0. Those employed in the PHARMACEUTICAL INDUSTRY are highly motivated. Q39.0. Those employed in the PHARMACEUTICAL INDUSTRY have a comfortable and safe working environment. Q40.0. Those employed in the PHARMACEUTICAL INDUSTRY receive adequate job focused training. Q41.0. Those employed in the PHARMACEUTICAL INDUSTRY generally work in one site/office location and seldom travel for work. Q42.0. Those employed in the PHARMACEUTICAL INDUSTRY feel that their job offers sufficient challenges. Q43.0. The CONSTRUCTION INDUSTRY is flexible. Q44.0. The CONSTRUCTION INDUSTRY is profit focused. Q45.0. The CONSTRUCTION INDUSTRY is contractual. Q46.0. The CONSTRUCTION INDUSTRY is insular. Q47.0. The CONSTRUCTION INDUSTRY is efficient. Q48.0. The CONSTRUCTION INDUSTRY is research lead. Q49.0. The CONSTRUCTION INDUSTRY is highly regulated. Q50.0. The CONSTRUCTION INDUSTRY is adequately resourced. Q51.0. The CONSTRUCTION INDUSTRY is proactive. Q52.0. The CONSTRUCTION INDUSTRY is highly technological. Q53.0. Those employed in the CONSTRUCTION INDUSTRY Have low job related stress. Q54.0. Those employed in the CONSTRUCTION INDUSTRY have high job satisfaction. Q55.0. Those employed in the CONSTRUCTION INDUSTRY Receive good pay/employment packages. Q56.0. Those employed in the CONSTRUCTION INDUSTRY are highly motivated. Q57.0. Those employed in the CONSTRUCTION INDUSTRY have a comfortable and safe working environment. Q58.0. Those employed in the CONSTRUCTION INDUSTRY receive adequate job focused training. Q59.0. Those employed in the CONSTRUCTION INDUSTRY generally work in one site/office location and seldom travel for work. Q60.0. Those employed in the CONSTRUCTION INDUSTRY feel that their job offers sufficient challenges.

9.4 Questionnaire Analysis

The questionnaire data was analysed by two main statistical methods, univeriate descriptive statistics and bivariate correlations.

The statistical analysis of the questionnaire data is dependant on the type of measurement scale used to obtain the data[2]. Descriptive statistics are used to analyse the nominal and ordinal data obtained from the questionnaire. Frequency tables are used as means of showing how frequently each respondent gave a response and percentages are generated based on valid responses. Cross tabulations were produced for the comparison of the nominal variables of the construction and pharmaceutical groupings.

Bar charts are a suitable way of displaying nominal and ordinal data and have therefore been used to display a number of the survey results. Cluster bar charts have been included as they clearly illustrate the results of the cross tabulations of two nominal variables, in this case construction and pharmaceutical respondent groups. The cross tabulations produced are a convenient way of displaying the distribution of independent and dependant variables and the strength and direction of the variables relationship or *correlation.*

Correlation tests were run using the SPSS software package. The test aim was to investigate the relationship between the practitioner's experience of validation with the other data categories that emerged from the case studies and literature. Correlation as an analysis tool allows the researcher to measure and determine the strength of relationship between two variables. The computed correlation coefficient called Pearson's correlation coefficient (r) is used and varies between -1 and +1. The distance from zero indicates the strength of correlation and the sign indicates a positive or negative relationship i.e. agreement or disagreement. The SPSS software package also calculates the significance (p) of the relationship. The significance of correlations at the 0.05 level are indicated by a single asterisk* and those significant at the 0.01 level are noted by two asterisks**.

[2] See section 5.16 for discussion of nominal, ordinal and interval measurements.

The results of the questionnaire responses are discussed below:

9.4.1 Experience of Respondents

The number of year's experience of the respondents is tabulated in figures 9.2 and 9.3. All of the construction respondents have more than ten year's industrial experience with 36.4% having more than twenty years.

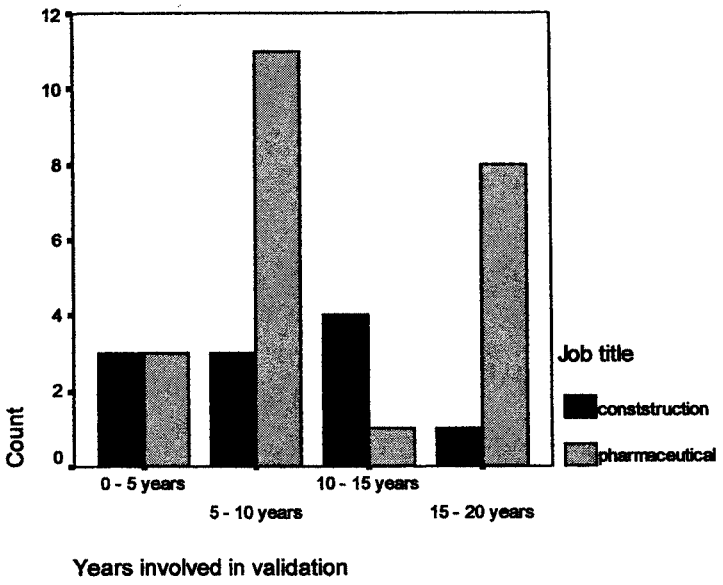
Fifty-six and a half percent of the pharmaceutical sector respondents have more than twenty years experience with only 8.7% having less than ten year's.

Over half of the survey, both construction and pharmaceutical sectors, had less than ten years direct validation experience (construction 54.6%, pharmaceutical 60.8%).

Figure 9.2 Number of Years involved in the construction or pharmaceutical industry

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
Construction	Valid	10 - 20 years	7	63.6	63.6	63.6
		20 - 30 years	2	18.2	18.2	81.8
		30 - 40 years	2	18.2	18.2	100.0
		Total	11	100.0	100.0	
Pharmaceutical	Valid	0 - 5 years	2	8.7	8.7	8.7
		10 - 20 years	8	34.8	34.8	43.5
		20 - 30 years	10	43.5	43.5	87.0
		30 - 40 years	3	13.0	13.0	100.0
		Total	23	100.0	100.0	

Figure 9.3: Number of Years involved in validation



9.4.2 Experience Category

Figure 9.4 shows correlations between the variables of timing, implementation, cost and quality with that of experience. The measurement proposition relationship column indicates the bivariate analysis of experience and a specific category question that is denoted by a prefix Q, which represents a questionnaire proposition or question. Each question belongs to one of the category groupings set out in figure 9.1.

Figure 9.4: Summary of Experience Correlations

Variable	Measurement Proposition Relationship	Construction	Pharmaceutical
Timing	Between (b) and Q11.0	Pearson r -.0.106 Sig.(2 tailed) 0.756	Pearson r - 0.513* Sig.(2 tailed) 0.012
Implementation	Between (b) and Q12.0	Pearson r 0.008 Sig.(2 tailed) 0.981	Pearson r 0.438* Sig.(2 tailed) 0.012
Cost	Between (b) and Q6.0 and Q6.1 and Q6.2 and Q6.3 and Q6.4	Pearson r 0.893** Sig.(2 tailed) 0.003 Pearson r - 0.289 Sig.(2 tailed) 0.488 Pearson r - 0.846* Sig.(2 tailed) 0.016 Pearson r - 0.370 Sig.(2 tailed) 0.413 Pearson r 0.056 Sig.(2 tailed) 0.906	Pearson r 0.081 Sig.(2 tailed) 0.766 Pearson r 0.173 Sig.(2 tailed) 0.537 Pearson r 0.322 Sig.(2 tailed) 0.225 Pearson r 0.442 Sig.(2 tailed) 0.087 Pearson r 0.624* Sig.(2 tailed) 0.013
Quality	Between (b) and Q9.3 and Q10.1 and Q15.0	Pearson r 0.754** Sig.(2 tailed) 0.007 Pearson r 0.685* Sig.(2 tailed) 0.020 Pearson r - .0.068 Sig.(2 tailed) 0.844	Pearson r 0.185 Sig.(2 tailed) 0.398 Pearson r -.0.245 Sig.(2 tailed) 0.259 Pearson r - 0.434* Sig.(2 tailed) 0.039

The correlation between *timing* of the validation process and *experience* gives a common negative correlation between sectors. The negative correlation of commencement of validation at the design stage is correlated more strongly by the pharmaceutical respondents ($r = -0.513$, $p = 0.012$) than the construction respondents ($r = -0.106$, $p = 0.756$). However a two tailed significance of 0.756 does not represent a strong relationship.

The relationship between *experience* and the *implementation* proposition that, the validation works normally starts when all construction activities are complete so as to allow the installation work to proceed without interruption, correlated positively ($r = 0.438$, $p = 0.012$) in the pharmaceutical replies.

The correlation calculation results for *validation cost* and *experience* produced an opposite relationship between the two sectors. A low cost, below 5%, received a strong correlation in the construction sector ($r = 0.893$, $p = 0.003$) as opposed to a weak pharmaceutical correlation. A cost of above 20% received a strong correlation in the pharmaceutical sector ($r = 0.624$, $p = 0.013$) and a weak construction correlation. The strength of relationship weakened with each incremental reduction in perceived validation cost for the pharmaceutical respondents. The construction

respondents' correlation of cost and experience gave a strong positive relationship for costs of below 5%. A strong negative relationship of perceived cost of between 10% to 15% and experience produced a correlation of $r = -0.846$ and $p = 0.013$. This gives an indication that construction and pharmaceutical sectors view the magnitude of cost differently. This underlines the view of writers such as Bender (1996) who argue cost data sharing is uncommon between groups.

For the construction sector, geographic location and its effect on regulations correlated strongly with *experience* ($r = 0.754$, $p = 0.007$). This was not the case for the pharmaceutical sector ($r = 0.185$, $p = 0.398$). See appendix C for full SPSS reports.

With reference to the cybernetic model, the literature survey and case study data present a common reoccurring theme that regulatory information sits in or closer to the pharmaceutical environment, rather than in the construction environment.

The construction respondent's showed a strong correlation between experience and regulatory compliance. When asked to rank the proposition; a validated facility is considered compliant when it is completed on time and at no additional cost, the correlation obtained was positive ($r = 0.685$, $p = 0.020$). This may help to explain the, perhaps, differing view of *quality* within the grouping sector.

9.4.3 Complexity Category

With reference to figure 9.5, the cross tabulation shows that the implementation of the validation activity is considered more complex by the pharmaceutical respondents than the construction respondents (pharmaceutical 60.9% and construction 36.4%). This result may indicate limited knowledge or experience within the construction group and the pharmaceutical sector's awareness of the impact of manufacturing complexity on sub-systems.

Figure 9.5: Validation is complex to implement

Job title			Freq	Percent	Valid Percent	Cumulative Percent
Construction	Valid	SA	2	18.2	18.2	18.2
		A	2	18.2	18.2	36.4
		N	4	36.4	36.4	72.7
		D	3	27.3	27.3	100.0
		Total	11	100.0	100.0	
Pharmaceutical	Valid	A	14	60.9	60.9	60.9
		N	6	26.1	26.1	87.0
		D	2	8.7	8.7	95.7
		SD	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

Freq = Frequency

Figure 9.6 shows correlations between the variables of *timing, implementation, cost* and *quality* with *complexity* for each industry sector. The strongest correlation is between *complexity* and the quality proposition that validation is only required if the pharmaceutical client asks for it. The construction sector relationship between complexity and quality has a positive correlation ($r = 0.772$, $p = 0.009$). *Complexity* and *cost* correlated positively for both industry sectors. With reference to the propositions of validation being complex to implement and validation being expensive to implement the construction correlation ($r = 0.682$, $p = 0.021$) was slightly stronger than that of the pharmaceutical industry ($r = 0.461$, $p = 0.027$). This underlines that the case studies may corroborate with the view of the literature that indicates pharmaceutical processes are complex and highly technological.

Figure 9.6: Summary of Complexity Correlations

Variable	Measurement Proposition Relationship	Construction	Pharmaceutical
Implementation	Between Q2.2 and Q3.0.	Pearson r 0.187 Sig.(2 tailed) 0.582	Pearson r 0.491* Sig.(2 tailed) 0.017
Cost	Between Q2.2 and 2.3 Between Q2.2 and Q4.0	Pearson r 0.682* Sig.(2 tailed) 0.021 Pearson r 0.303 Sig.(2 tailed) 0.395	Pearson r 0.461* Sig.(2 tailed) 0.027 Pearson r 0.462* Sig.(2 tailed) 0.031
Quality	Between Q2.2 and Q2.0	Pearson r 0.772** Sig.(2 tailed) 0.009	Pearson r -. 0.052 Sig.(2 tailed) 0.813

A positive relationship between *complexity of implementation* and *validation cost* being difficult to estimate was recorded in the pharmaceutical responses ($r = 0.462$, $p = 0.031$). Complexity and estimation of duration were positively correlated in both sectors (construction $r = 0.187$, $p = 0.582$ and pharmaceutical $r = 0.491$, $p = 0.017$).

9.4.4 Timing Category

Both groups are in some agreement with the time category statement that the design/construction team is rarely involved with the clients QA team early in the project (construction 54.5%, pharmaceutical 52.2%). See Figure 9.7.

Figure 9.7: The design/construction team is rarely involved with the clients QA team early in the project.

Job title			Freq	Percent	Valid Percent	Cumulative Percent
Construction	Valid	SA	1	9.1	9.1	9.1
		A	5	45.5	45.5	54.5
		D	4	36.4	36.4	90.9
		SD	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
Pharmaceutical	Valid	A	12	52.2	52.2	52.2
		N	1	4.3	4.3	56.5
		D	7	30.4	30.4	87.0
		SD	3	13.0	13.0	100.0
		Total	23	100.0	100.0	

Freq = Frequency

Figure 9.8 shows the response to the proposition that validation normally starts at the initial design stages of a facility project. Both responses indicate agreement, with the pharmaceutical sector clearly indicating early involvement (pharmaceutical 87%, construction 54.5%). However, the level of disagreement to the proposition is higher in the construction sector (construction 36.4%, pharmaceutical 8.7%).

Figure 9.8: Validation normally starts at the initial design stages of a facility project.

Job title			Freq	Percent	Valid Percent	Cumulative Percent
Construction	Valid	SA	1	9.1	9.1	9.1
		A	5	45.5	45.5	54.5
		N	1	9.1	9.1	63.6
		D	4	36.4	36.4	100.0
		Total	11	100.0	100.0	
Pharmaceutical	Valid	SA	13	56.5	56.5	56.5
		A	7	30.4	30.4	87.0
		D	2	8.7	8.7	95.7
		SD	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

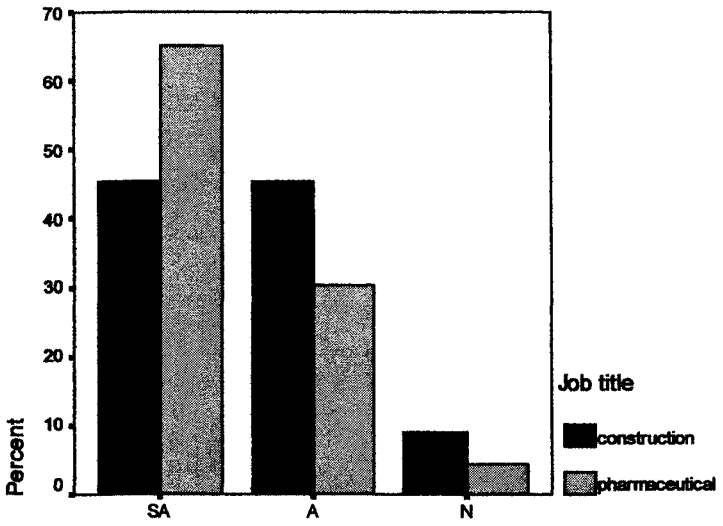
Both sectors strongly agree that the timing of implementation is crucial to the success of the construction project (construction 90.9%, pharmaceutical 95.5%). However, project success may be measured differently by industry sectors[3].

9.4.5 Partnering Category

Figure 9.9 shows the level of agreement between groups for the adoption of partnering agreements. Both sectors indicated an agreement with the proposition that projects run more smoothly when an integrated/partnering approach is adopted. (i.e. all those involved with any aspect of the project have an input into the project, including validation at an early stage) (Q21.0) of more than 90%.

[3] See section 9.4.2.

Figure 9.9: Projects run more smoothly when an integrated/partnering approach is adopted. i.e. all those involved with any aspect of the project have an input into the project, including validation at an early stage.



9.4.6 Implementation Category

The planning of the duration of the validation activity is considered difficult by those in the construction industry sector (63.6%) but less so by the pharmaceutical sector illustrating an agreement of 43.5% and disagreement of 43.5%. A correlation of the pharmaceutical sector with estimation of duration produced a negative relationship ($r = -0.505$, $p = 0.014$) indicating that estimation is a project task that is clearly understood.

The survey strongly agreed with the statement that facility validation adds to overall project duration, although there was a small disagreement with this proposition by those in the pharmaceutical sector which equated to 21.7%. This is displayed in figure 9.10.

Unrealistic documentation requirements, excessive validation caused by neglecting system impact assessments and, as previously noted by James (1998), understanding the amount and timing of the process, appear to be factors which have help perpetuate this view.

Figure 9.10: Facility validation duration - adds to overall project duration

Job title			Freq	Percent	Valid Percent	Cumulative Percent
Construction	Valid	SA	2	18.2	18.2	18.2
		A	8	72.7	72.7	90.9
		N	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
Pharmaceutical	Valid	SA	2	8.7	8.7	8.7
		A	15	65.2	65.2	73.9
		N	1	4.3	4.3	78.3
		D	3	13.0	13.0	91.3
		SD	2	8.7	8.7	100.0
		Total	23	100.0	100.0	

Freq = Frequency

With regards to timing of implementation, both sectors greatly disagreed with the proposition that validation should commence after the construction activities (construction 72.7%, pharmaceutical 82.6%).

When asked to rank the proposition that most construction companies are not sufficiently experienced to complete the validation of a facility (i.e. writing protocols, carrying out tests and reporting outcomes) both sets of respondents were in agreement with the statement (construction 63.6%, pharmaceutical 56.5%). This reveals that the construction sector believes the validation task to be one that resides in the pharmaceutical environment.

When asked to consider the proposition regarding process change control (shown in figure 9.11) construction respondents noted that there were sufficient change control mechanisms in place (63.6%) whilst the pharmaceutical sector gave a weaker response showing that this may not be the case. Both groups produced quite high percentages in the *neither agree nor disagree* rank classification.

The change control process is better defined in the pharmaceutical environment for the reason of regulatory compliance[4]. The ability to recognize, asses and record change is central to maintaining a validated system. Change implementation suffers from unauthorized system replacement or modification from those who are unaware of the importance of change. One reason why the construction group considered that there are sufficient systems in place may be explained by limited boundary adaptation. The pharmaceutical group's response was less positive than expected; this may be related to the common problems that exist in implementing appropriate site wide change systems and problems of internal and external unauthorized change. This problematic theme also emerged from case study A, where design changes were not appropriately assessed and so adversely impacted on project schedule and cost.

Figure 9.11: During the facility validation there are usually sufficient systems in place to allow feedback and corrective action if something has been incorrectly designed, installed or commissioned

Job title			Freq	Percent	Valid Percent	Cumulative Percent
Construction	Valid	SA	1	9.1	9.1	9.1
		A	6	54.5	54.5	63.6
		N	3	27.3	27.3	90.9
		D	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
Pharmaceutical	Valid	SA	3	13.0	13.6	13.6
		A	9	39.1	40.9	54.5
		N	4	17.4	18.2	72.7
		D	4	17.4	18.2	90.9
		SD	2	8.7	9.1	100.0
		Total	22	95.7	100.0	
	Missing	.00	1	4.3		
	Total		23	100.0		

Freq = Frequency

9.4.7 Cost Category

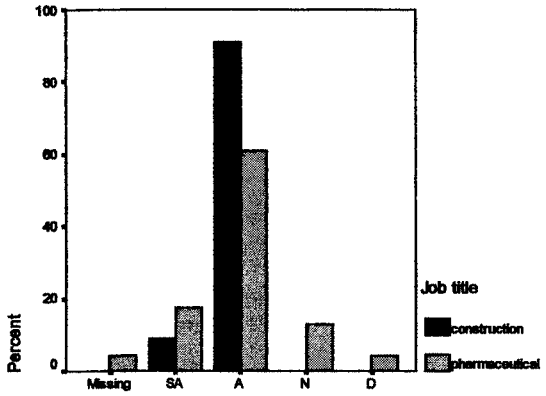
The construction sector viewed the *implementation of validation* to be more *expensive* (63.6%) than those in the pharmaceutical sector (47.8%).

Both industrial sectors displayed some unfamiliarity with *cost planning of validation* as relatively high percentages were noted in the rank of neither agree nor disagree (construction 27.3%, pharmaceutical 34.8%).

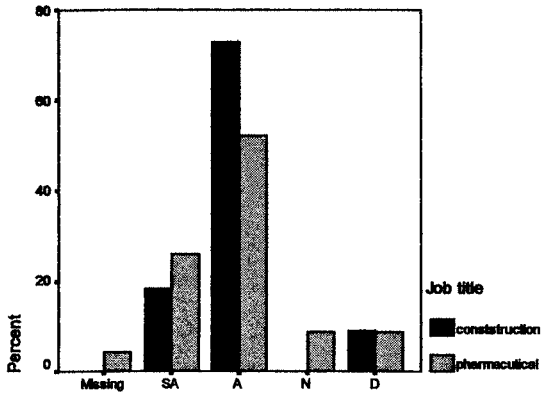
[4] See section 3.11.

60 % of contracting organizations indicated that facility validation cost is difficult to estimate whilst 40% disagreed. There was no clear agreement by the pharmaceutical organizations that again scored relatively highly in the neither category (18.2%) The methods used within organizations to plan their validation project budgets was examined by making a number of proposals on the common methods of cost planning highlighted in the literature in section 3.12.

Figure 9.12a: Calculation of validation cost



Calculation based on - past experience



Calculation based on - planning matrix

Figure 9.12b: Calculation of validation cost

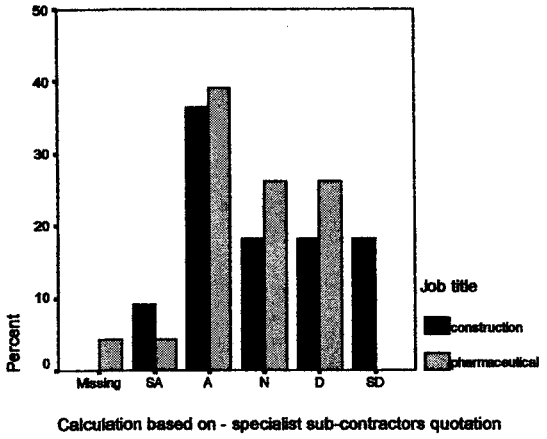


Figure 9.12c: Calculation of validation cost

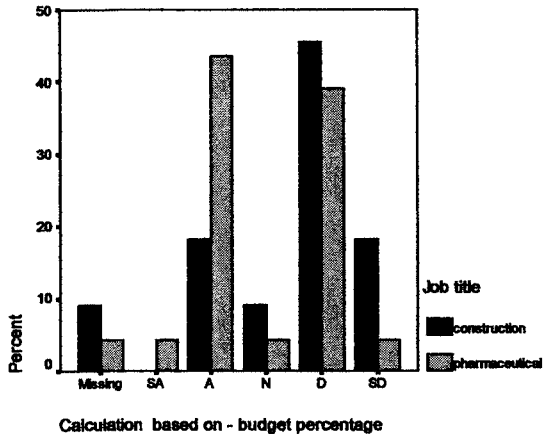


Figure 9.12d: Calculation of validation cost

Figure 9.12 illustrates that the most common methods of calculating validation costs are in line with the literature, by a *planning matrix* constructed through *previous experience* of the process. Construction respondents reported that 100% of all estimates of cost were based on *past experience*. Pharmaceutical respondents indicated that a lower figure of 81.8%. Both sectors indicated that *planning matrices* are used to calculate validation costs (construction 90.9%, pharmaceutical 81.8%) rather than budget percentages, sub-contractor quotations and the time available in the commissioning phase of the project.
Fieldwork data obtained from case studies A and B also showed that 'check matrix' systems were utilized in planning.

A strong and significant correlation between the *cost measurement* proposition, that *validation cost* is difficult to estimate and the *implementation category* proposition

that validation duration is also difficult to estimate, was calculated in the pharmaceutical sector ($r = 0.776$, $p = 0.00$). This may imply that the planning process is complex to implement due to the number of the various project groups and the project managers' limited understanding of their inputs.

9.4.8 Quality Category

Both industry groups are in strong agreement that validation is an essential requirement for *regulatory compliance* (construction 90.9%, pharmaceutical 100%) and is a legal obligation even if not asked for by a client (construction 60%, pharmaceutical 91.3%).

A significant number, 45.5% of construction respondents viewed the regulations governing the validation of pharmaceutical facilities as being difficult to understand. Over thirty six percent disagreed that regulations are complicated and 18.2% of the construction group neither agreed nor disagreed. Over half of pharmaceutical respondents (52.1%) considered pharmaceutical regulations to be understandable. Together with the case study data[5] this indicates that relevant regulatory and guidance information sits closer to those in the pharmaceutical environment. When asked to rank the statement that regulations are too general and not detailed enough, the construction response was one of slight agreement (9.1%). Pharmaceutical responses produced a small disagreement of 8.7%. Both groups ranked high in the neither category (construction 54.5%, pharmaceutical 26.1%).

Both statements regarding difficulty of understanding and regulation detail produced strong significant positive correlations in both groups (construction $r = 0.787$, $p = 0.004$ and pharmaceutical $r = 0.771$, $p = 0.000$). See figure 9.13.

[5] See section 8.10.

Figure 9.13: Summary of Quality Correlations

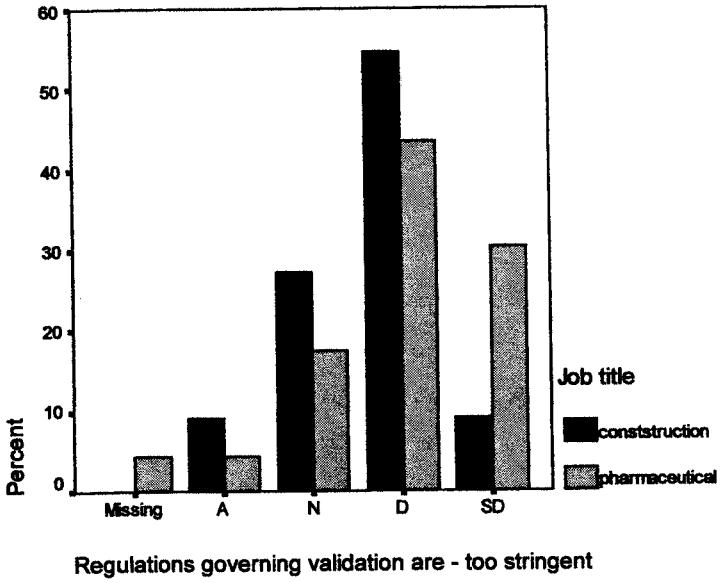
Variable	Measurement Proposition Relationship	Construction	Pharmaceutical
Quality	Between Q 7.2 and Q 7.3	Pearson r 0.516 Sig.(2 tailed) 0.104	Pearson r 0.550** Sig.(2 tailed) 0.006
	Between 7.2 and Q7.6	Pearson r 0.373 Sig.(2 tailed) 0.259	Pearson r 0.550** Sig.(2 tailed) 0.006
	Between Q7.3 and Q7.5	Pearson r 0.060 Sig.(2 tailed) 0.860	Pearson r 0.617** Sig.(2 tailed) 0.002
	Between Q 9.0 and Q9.1	Pearson r 0.677* Sig.(2 tailed) 0.022	Pearson r 0.075 Sig.(2 tailed) 0.739
	Between Q 9.0 and Q 9.3	Pearson r 0.731* Sig.(2 tailed) 0.011	Pearson r – 0.156 Sig.(2 tailed) 0.488
	Between Q 9.1 and Q 9.2	Pearson r 0.787** Sig.(2 tailed) 0.004	Pearson r 0.771** Sig.(2 tailed) 0.000
	Between Q 9.1 and Q 9.3	Pearson r 0.694* Sig.(2 tailed) 0.018	Pearson r 0.427* Sig.(2 tailed) 0.042
	Between Q 9.1 and Q 9.4	Pearson r 0.581 Sig.(2 tailed) 0.061	Pearson r 0.693** Sig.(2 tailed) 0.000
	Between Q 9.3 and Q 9.4	Pearson r 0.752** Sig.(2 tailed) 0.008	Pearson r 0.413 Sig.(2 tailed) 0.050

Forty three percent of pharmaceutical respondents disagreed with the proposition that pharmaceutical regulations vary from country to country whilst 36.4% of the construction respondents agreed that this was the case. Both groups also reported large numbers of neither ranking percentages (construction 27.3%, pharmaceutical 39.1%). The proposition that *geographical location* has an effect on compliance correlated strongly with that of *difficulty of understanding* regulations in the construction sector ($r = 0.694$, $p = 0.018$). In the pharmaceutical sector a positive correlation was also noted ($r = 0.427$, $p = 0.042$).

When propositioned with regards to availability of standards and regulations the construction group considered regulations less easily obtainable than the pharmaceutical group (construction 54.6%, pharmaceutical 73.9%). Again both ranks in the neither category were relatively high (construction 45.5 %, pharmaceutical 26.2%).

With reference to figure 9.14, 77.3% of the pharmaceutical sector and 53.4% of the construction sector indicated that regulations governing pharmaceutical facility validation are not too stringent.

Figure 9.14: Regulations governing validation are too stringent.



A significant proportion of the construction sector acknowledged that GMP regulations are not easily understood or obtainable and, to a small degree, consider them general and lacking in detail. A moderate proportion of the construction sector also perceived that regulations vary with geographic region. The pharmaceutical view differed with that of the construction group indicating that the regulatory environment is reasonably well understood and uncomplicated.

Understanding of pharmaceutical compliance was examined by asking respondents to rank four different propositions with regards to the meaning of regulatory compliance.

The propositions were as follows:

Q10.0 A validated facility is considered compliant when it - fulfils the requirements of the initial design.

Q10.1 A validated facility is considered compliant when it - is completed on time and at no additional cost.

Q10.2 A validated facility is considered compliant when it - satisfies the client.

Q10.3 A validated facility is considered compliant when it - satisfies the regulatory inspection.

With respect to Q10.0, 54.5% of construction and 82.6% of pharmaceutical responses agreed with the statement that a compliant facility was one that fulfils the requirements of the initial design. Both groups disagreed with Q10.1, that regulatory compliance results from the facility being completed on time and at no additional cost (construction 90.9%, pharmaceutical 87.0%). The response to the proposition of regulatory compliance is based on client satisfaction, Q10.2, established a common opinion between the groups. In the construction group, 54.5% disagreed, 36.4% ranked in the neither category and 9.1% slightly agreed. 43.5% of the pharmaceutical group agreed and 56.5% disagreed with the statement. The final statement suggesting compliance results in satisfactory regulatory inspection produced very high percentages of agreement in both groups (construction 100%, pharmaceutical 91.3%).

Over half of the survey thought that facility validation should be the responsibility of the whole project team and should not be left to the client (construction 63.6%, pharmaceutical 60.9%). Continued maintenance was considered an essential part of sustaining a facilities validated status (construction 81.8%, pharmaceutical 87.0%).There was general disagreement with the statement that facility validation is a new area of quality assurance that does not have clear industry guidelines (construction 72.7%, pharmaceutical 78.3%).

When questioned as to which areas of a pharmaceutical manufacturing site require validation, 27.3% of the construction sector neither agreed nor disagreed that restaurants require validation and 72.7% disagreed.100% of the pharmaceutical group reported that facility restaurants do not require any form of validation and both groups generally agreed that office spaces did not require any validation testing. The construction and pharmaceutical groups agreed (100%) that product manufacturing and product packaging areas require validation. There was a general uncertainty amongst the construction respondents with the question of validating general circulatory areas. Sixty three percent of the group indicated a neither rank, with equal

percentage of the remainder in agreement and disagreement. The pharmaceutical response was one of higher agreement that validation would be required (45%). However, 35% disagreed with this and 20% scored a neither ranking indicating an unsure overall response. Both groups agreed that dispensary areas require validation but when questioned about warehouse areas, the construction sector were less sure in their view indicating a 54.5% neither score as opposed to 100% agreement in the pharmaceutical sector.

There were strong positive correlations noted for the relationship between validation of offices and restaurants in both groups (construction $r = 0.939$, $p = 0.000$ and pharmaceutical $r = 0.935$, $p = 0.000$). Another notable correlation was evident between product manufacturing and packaging areas (construction $r = 0.516$, $p = 0.104$, pharmaceutical $r = 0.550$, $p = 0.006$). See appendix C for correlation reports. Together with investigating the areas of pharmaceutical facilities which require validation, propositions were made to examine the respondents' knowledge of what particular building elements may require validating. With reference to figures 9.15, 9.16, 9.17, 9.18, 9.19, and 9.20, the responses pointed to general agreement for the need to validate areas such as *internal construction materials, HVAC systems, room monitoring equipment, purified water systems* and *product contact gases*. General *indirect utility systems* were considered by the construction respondents to require validation (45.5%) although there was a quite high neither percentage (27.3%), indicating a degree of uncertainty. The pharmaceutical group's response indicated a slight disagreement with the statement that validation is required (52.2%).

Figure 9.15: With reference to Production/packaging product contact areas which of the following require validation - facility internal construction materials

Job title			Freq	Percent	Valid Percent	Cumulative Percent
Construction	Valid	SA	3	27.3	27.3	27.3
		A	6	54.5	54.5	81.8
		N	2	18.2	18.2	100.0
		Total	11	100.0	100.0	
Pharmaceutical	Valid	SA	16	69.6	69.6	69.6
		A	5	21.7	21.7	91.3
		N	2	8.7	8.7	100.0
		Total	23	100.0	100.0	

Freq = Frequency

Figure 9.16: With reference to Production/packaging product contact areas which of the following require validation - HVAC systems

Job title			Freq	Percent	Valid Percent	Cumulative Percent
Construction	Valid	SA	7	63.6	63.6	63.6
		A	3	27.3	27.3	90.9
		N	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
Pharmaceutical	Valid	SA	20	87.0	87.0	87.0
		A	3	13.0	13.0	100.0
		Total	23	100.0	100.0	

Freq = Frequency

Figure 9.17: With reference to Production/packaging product contact areas which of the following require validation - room monitoring systems

Job title			Freq	Percent	Valid Percent	Cumulative Percent
construction	Valid	SA	6	54.5	54.5	54.5
		A	4	36.4	36.4	90.9
		N	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
Pharmaceutical	Valid	SA	18	78.3	78.3	78.3
		A	5	21.7	21.7	100.0
		Total	23	100.0	100.0	

Freq = Frequency

Figure 9.18: With reference to Production/packaging product contact areas which of the following require validation - purified water systems

Job title			Freq	Percent	Valid Percent	Cumulative Percent
Construction	Valid	SA	7	63.6	63.6	63.6
		A	3	27.3	27.3	90.9
		N	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
Pharmaceutical	Valid	SA	22	95.7	95.7	95.7
		A	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

Freq = Frequency

9.19: With reference to Production/packaging product contact areas which of the following require validation - general indirect utility systems

Job title			Freq	Percent	Valid Percent	Cumulative Percent
construction	Valid	SA	2	18.2	18.2	18.2
		A	3	27.3	27.3	45.5
		N	3	27.3	27.3	72.7
		D	2	18.2	18.2	90.9
		SD	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
Pharmaceutical	Valid	SA	1	4.3	4.3	4.3
		A	7	30.4	30.4	34.8
		N	3	13.0	13.0	47.8
		D	6	26.1	26.1	73.9
		SD	6	26.1	26.1	100.0
		Total	23	100.0	100.0	

Freq = Frequency

Figure 9.20: With reference to Production/packaging product contact areas which of the following require validation - product contact gases

Job title			Freq	Percent	Valid Percent	Cumulative Percent
Construction	Valid	SA	7	63.6	63.6	63.6
		A	3	27.3	27.3	90.9
		N	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
Pharmaceutical	Valid	SA	21	91.3	91.3	91.3
		A	2	8.7	8.7	100.0
		Total	23	100.0	100.0	

Freq = Frequency

In relation to the regulatory compliance and quality survey questions above, the survey has established that there is a difference between the two industry groups. The construction industry responses indicate a moderate level of understanding of quality practices in the task environment. The pharmaceutical industry responses highlight a higher level understanding of the validation process.

9.4.9 Commissioning

The survey groups were presented with a number of statements regarding the role of commissioning. The first propositioned that commissioning should be used to qualify non-critical systems and the second and third suggested that good commissioning and recording of results could effectively be used instead of validation. The respondents were of the same opinion that high quality commissioning could not negate the need for a validation process and that non-critical systems should only be commissioned. When asked if good quality commissioning documentation could be used in-lieu of validation documentation 30.4% of the pharmaceutical group agreed and 18.2% of the construction group also agreed and 18% ranked the statement in the neither category.

9.5 Analysis Section Two - Culture and Attitudes

The second section of the survey questionnaire examines the attitudes each respondent has to his/her industry group and also to the other industry sector. Statements relating to industry characteristics such as flexibility, resource, technology, satisfaction, motivation etc were ranked by respondents. The information derived allowed the views and attitudes of both industry sectors to be gauged and this data allowed the constructs of the model of the validation process to be informed. The responses to section two of the industry survey are described in the following section:

When asked to rank the flexibility of the pharmaceutical industry both groups disagreed that that the pharmaceutical industry was flexible (construction 45.5%, pharmaceutical 60.8%). Significant percentages were recorded in the neither category (construction 30%, pharmaceutical 26.1%) indicating some uncertainty. 40% of construction respondents reported the construction industry as flexible while 60% of the pharmaceutical group considered the construction industry as more flexible. Neither category ranking was high for the construction respondents (40%) and moderate for the pharmaceutical respondents (25%). Figure 9.21 and 9.22 show the industry response.

Figure 9.21: Industry perceptions of flexibility (pharmaceutical)

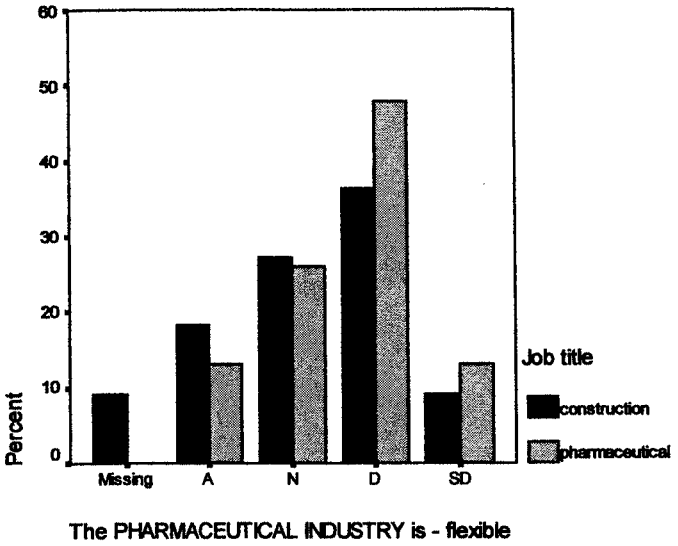
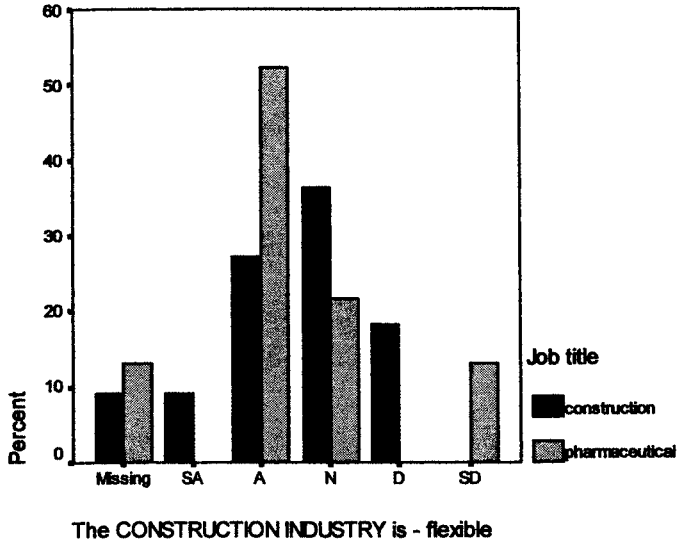


Figure 9.22: Industry perceptions of flexibility (Construction)



The pharmaceutical and construction industries are both seen as being highly profit focused. Over seventy two percent of the construction group and 73.9% of the pharmaceutical group agree or strongly agree with the proposition that the construction industry is profit focused. The firm response in the pharmaceutical sector is indicated by a low neither ranking of 4.3% compared to a higher 18.2% ranking in the construction sector. Both sectors view the profit focus higher in the construction industry than the pharmaceutical industry (construction 81.8%, pharmaceutical 100%).

Both industry sectors view the pharmaceutical industry as being highly regulated (construction 90.9%, pharmaceutical 100%). Thirty six percent of the construction industry considers itself highly regulated while 42.9% of the pharmaceutical industry indicated they believed there were significant levels of construction industry regulation. A negative correlation of pharmaceutical industry sector with the statement of the construction industry being highly regulated ($r = -0.520$, $p = 0.016$) was computed.

Seventy percent of construction respondents indicated no response to the proposition that the pharmaceutical industry is contractual, while over half (52.2%) of the pharmaceutical group were in agreement with the statement or indicated a neither ranking (30.4%). 90.9% of construction and 90.5% of pharmaceutical respondents did however see the construction industry as being contractual in nature. Again the low neither category rankings (construction 9.1%, pharmaceutical 9.5%) showed a firm response.

Those employed in the pharmaceutical sector viewed themselves as more insular than did the construction industry (pharmaceutical 56.5%, construction 30%). The strength of this view was however questionable as a very high neither category was obtained (40%). When propositioned that the construction industry is insular there was slight agreement in the construction group (36.4% agree, 18.2% disagree) and some disagreement in the pharmaceutical group (33.3% disagree, 23.8% agree). High neither classification was noted in both industry sectors (construction 45.5%, pharmaceutical 42.9%).

In terms of efficiency the pharmaceutical industry respondents viewed themselves as inefficient (69.6%). The response from the construction industry was mixed with some agreement of inefficiency (36.4%) and 54.5% of the group ranking in the neither category. Both groups noted construction industry efficiency as high in the neither category (construction 54.5%, pharmaceutical 47.6%), indicating a reasonably high degree of uncertainty in the response.

The survey respondents acknowledge the high level of research and development within the pharmaceutical sector. Both survey groups agree that the pharmaceutical industry is research lead. The opposite view in the construction industry is held by both groups. See figure 9.23 and 9.24 below.

Figure 9.23: The PHARMACEUTICAL INDUSTRY is - research lead

Job title			Freq	Percent	Valid Percent	Cumulative Percent
Construction	Valid	A	6	54.5	54.5	54.5
		N	5	45.5	45.5	100.0
		Total	11	100.0	100.0	
Pharmaceutical	Valid	SA	7	30.4	30.4	30.4
		A	11	47.8	47.8	78.3
		N	4	17.4	17.4	95.7
		D	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

Freq = Frequency

Figure 9.24: The CONSTRUCTION INDUSTRY is - research lead

Job title			Freq	Percent	Valid Percent	Cumulative Percent
Construction	Valid	N	3	27.3	27.3	27.3
		D	5	45.5	45.5	72.7
		SD	3	27.3	27.3	100.0
		Total	11	100.0	100.0	
Pharmaceutical	Valid	N	1	4.3	4.8	4.8
		D	10	43.5	47.6	52.4
		SD	10	43.5	47.6	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

Freq = Frequency

There was a strong positive correlation, (in the pharmaceutical sample), between the pharmaceutical industry being research lead with levels of high technology ($r = 0.536$, $p = 0.008$). Also in relation to this proposition there was positive correlation noted in the construction sector ($r = 0.664$, $p = 0.026$).

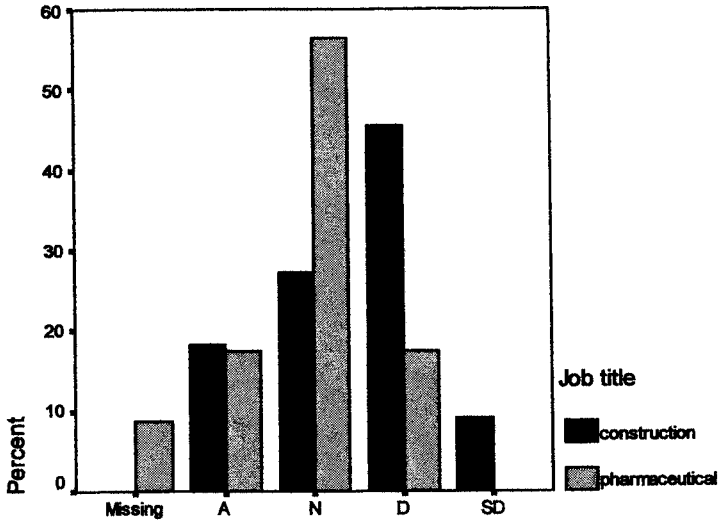
Both groups also view the construction industry as not being highly technological. The construction group view is that there is a higher implementation of complex technologies in the pharmaceutical sector (72.7%). 52.2% of the pharmaceutical industry survey group considers itself highly technological. Levels of high technology also correlated positively with efficiency ($r = 0.497$, $p = 0.016$).

When propositioned on resource allocation, the construction group perceived the pharmaceutical group as being adequately resourced (72.7%). Only 43.5% of pharmaceutical respondents indicated that resources were adequate, with 30.4% disagreeing with the proposition and 26.1% indicating a neither category. The construction sector saw itself as being inadequately resourced (54.5%) and 42.8% of the pharmaceutical survey group also indicated this was the case. Both groups scored reasonably high in the neither category (construction 36.4%, pharmaceutical 42.9%).

The final section of the industry questionnaire investigated the attitudes both groups had about their individual profession within their industry sector and also the perceived view of those working in the other industry.

The pharmaceutical group strongly disagreed (86.9%) with the proposition that those in the pharmaceutical industry have low job related stress, while there was some agreement in the construction group with regards to low pharmaceutical industry stress levels (27.3%). Those in the construction industry reported high levels of stress (72.7%). 61.9% of the pharmaceutical group viewed that this was in fact the case. Nearly half of the pharmaceutical and construction respondents (47.8%, 45.5%) considered that the pharmaceutical industry has high levels of job satisfaction. Construction industry job satisfaction was rated more strongly by the construction sector (63.6%) and 33.3% of the pharmaceutical sector was in agreement however a large percentage indicated a neither category (57.1%).
Employment and pay packages in the pharmaceutical industry were perceived by both industry sectors as good (construction 72.7%, pharmaceutical 65.2%). Construction employment and pay packages were noted as less attractive with 54.6% of the construction group in disagreement with the proposition see figure 9.25. Industry group construction correlated negatively with pay and employment package ($r = -0.741$, $p = 0.009$)

Figure 9.25: Construction - receive good pay/employment packages



CONSTRUCTION - receive good pay/employment package

Reported motivation within the construction and pharmaceutical industries are tabulated in Figures 9.26 and 9.27.

Figure 9.26: Those employed in the CONSTRUCTION INDUSTRY - are highly motivated

Job title			Freq	Percent	Valid Percent	Cumulative Percent
Construction	Valid	A	5	45.5	45.5	45.5
		N	3	27.3	27.3	72.7
		D	3	27.3	27.3	100.0
		Total	11	100.0	100.0	
Pharmaceutical	Valid	A	4	17.4	19.0	19.0
		N	13	56.5	61.9	81.0
		D	4	17.4	19.0	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

Freq = Frequency

Figure 9.27: Those employed in the PHARMACEUTICAL INDUSTRY - are highly motivated

Job title			Freq	Percent	Valid Percent	Cumulative Percent
Construction	Valid	SA	1	9.1	9.1	9.1
		A	4	36.4	36.4	45.5
		N	6	54.5	54.5	100.0
		Total	11	100.0	100.0	
Pharmaceutical	Valid	SA	1	4.3	4.3	4.3
		A	7	30.4	30.4	34.8
		N	11	47.8	47.8	82.6
		D	3	13.0	13.0	95.7
		SD	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

Freq = Frequency

The construction industry respondents agree that significant proportions (45.5%) of those employed in the construction and pharmaceutical industries are highly motivated. 34.8% of pharmaceutical respondents agree that those employed in pharmaceutical industry are highly motivated. Their view of motivation in the construction industry is one of uncertainty (neither 61.9%).

Working conditions in the pharmaceutical sector are seen by both industries as comfortable and safe (construction 63.6%, pharmaceutical 65.2%) as opposed to working conditions in the construction industry which are not considered in the same vein (construction 54.5%, pharmaceutical 52.3%).

The majority of those surveyed agreed that the construction sector does not generally work in one office or site location and do travel greater distances to work (construction 81.8%, pharmaceutical 95.2%).

45.5 % of those in the construction sector agreed that the pharmaceutical group do work in one specific location and do not travel great distances to the work place.

Both industries also agree that the pharmaceutical industry does receive adequate job focused training (construction 72.7%, pharmaceutical 69.5%). 36.4% of the construction group indicated that the level of training in the construction industry is unsatisfactory and 54.5% responded in the neither category. A small percentage of those belonging to the pharmaceutical group disagreed that the construction industry received adequate training. A negative correlation between the pharmaceutical sector and training was recorded ($r = -0.518$, $p = 0.16$)

When propositioned about worked based challenges, the construction respondents indicated a slightly higher percentage agreement they had sufficient challenges in the work environment (construction 63.6%, pharmaceutical 52.2%).

9.6 Summary

In summary, the survey data has supported the findings from both the case study and interview data included in sections 6, 7 and 8, indicating a number of cultural differences between the two sectors. Survey respondents viewed the pharmaceutical industry as being technological and inflexible as well as highly regulated and committed to research and development.

The construction industry was perceived by the survey respondents as highly contractual, with low implementation of technology and research and development. Pharmaceutical facilities were considered complex by those in the construction sector.

Stress levels were reported as being higher in the construction sector. Employment packages were seen as slightly more attractive in the pharmaceutical sector and motivation was also rated as higher in this group. Good working conditions and training opportunities were noted in the pharmaceutical sector whilst working conditions and training ranked lower in the construction industry.

The survey also indicated limited project team integration, highlighting that over fifty percent of respondents believed that the client's quality and construction design groups rarely interface early in the project. Both sectors do however recognize the importance of early process implementation occurring before construction completion, although, it appears that the case studies suggest that this may not often occur.

From the survey data the validation process is viewed by the construction industry as being difficult to plan and expensive. The pharmaceutical industry views this process as less demanding and less costly. The survey data also established a difference between the perceived validation costs, with the pharmaceutical industry suggesting costs of the order of twenty percent and the construction industry considering costs to

be lower at five percent. There was a clear consensus ($r = 0.893$, $p = 0.003$) among respondents from the construction sector as opposed to a weak pharmaceutical sector correlation. Costs of above 20% received a strong correlation in the pharmaceutical sector ($r = 0.624$, $p = 0.013$) and less strong correlation in the construction sector. The reason appears to be linked to past experience of similar projects and gaining project based knowledge. This reason was also supported by case study contracting organizations who had limited pharmaceutical and healthcare construction experience.

The literature review and case studies has highlighted that many industry practitioners are unclear of 'which systems' and 'how much' validation testing is required. It also appears to be a contributory factor that underlines why the survey respondents considered that the validation process adds to the overall project schedule.

The effect of complexity on validation process costs was highlighted in the case studies where project data collection and control procedures were highlighted as being problematic factors in controlling the project. The positive correlation (pharmaceutical sector, $r = 0.682$, $p = 0.021$ and construction sector $r = 0.461$, $p = 0.027$) between *complexity* and *cost* in both industry sectors indicated a clear proportional relationship between cost and complexity of validation.

This chapter has presented the results and analysis of the survey which was obtained from construction and pharmaceutical respondents using the SPSS computer software package.

Conclusions with respect to the initial theoretical propositions and the cybernetic model, together with the empirical data sets from case studies A, B and C and the survey, are presented in Chapter Ten.

Chapter Ten: Discussion, Conclusions and Implications of the study

This chapter discusses the case study and survey evidence to address the initial propositions and research model.

10.1 Study Propositions

In chapter four, the cybernetic systems model of the validation process was constructed together with five related propositions. The propositions are composites of both endogenous and exogenous environmental relationships that influence transformation. The propositions are shown in figure 10.1

Figure 10.1: Summary of Study Propositions

Proposition	Theoretical Validation Themes
P1: System regulatory inputs are implicit and can result in embedded non-compliance which can affect the validated status of the facility and its building systems .Regulations are implied though not directly expressed and in effect cause GMP non-conformances.	Quality understanding, experience.
P2: The structure of the project team should be appropriate to the task environment	Planning (time and cost), communication, integration, resource.
P3: In order to maximise the potential success of the project the validation process should be controlled through feedback and sequencing of implementation tasks.	Task implementation, control, sequencing and change, partnering.
P4: The complexity of the validation testing procedures should be appropriate to the complexity of the systems in the task environment.	Complexity, project termination (start-up and commissioning).
P5: The desired system output, that of regulatory compliance, is affected by differing views of quality.	Culture and attitude, Quality understanding, experience.

The following section explains the proposition assessment procedure and interpretation of the results.

10.2.1 Proposition Assessment: P1

P1: *System regulatory inputs are implicit and can result in embedded non-compliance which can affect the validated status of the facility and its building*

systems. Regulations are implied though not directly expressed and in effect cause GMP non-conformances.

Considering the data derived from the questionnaire, the proposition can be considered to be supported. The construction sector demonstrated a limited understanding of project quality requirements associated with the provision of pharmaceutical buildings and the level of understanding of quality requirements was found to be higher in the pharmaceutical sector.

The reason for this may be partly related to the process of regulatory inspection and that the construction industry indicated in the survey that the regulations governing the process were difficult to understand ($r = 0.787$, $p = 0.004$).
Inspection and audit feedback will typically occur sometime after project completion and this information is disseminated to only part of the project team; the pharmaceutical client. The information is then fed into the pharmaceutical 'quality pool' and circulates within the industry environment predominantly through industry journals, training seminars and the knowledge of those in the environment. This data is unlikely to reach those who were responsible for the design and construction of the facility, resulting in limited scope for improvement in future pharmaceutical projects.

The proposition was also supported by the data analysis. Case study A demonstrated the presence of embedded non-compliances which were discovered sometime later by a quality audit and case C included significant embedded non-compliance that had major implications on the client's budget.

10.2.2 Proposition Assessment: P2

P2: *The structure of the project team should be appropriate to the task environment*

This proposition was supported by the case study data. In case A the validation project team consisted of a wide range of participants with skills in areas such chemical engineering, biology, and general engineering. The project group skills

were not suitable to test buildings and building systems. The level of project group skills were mismatched with those required to understand, produce and execute validation protocols. The client's validation manager who was responsible for employing the validation service provider was also unfamiliar with construction techniques and HVAC technology. The associated communications problems between the validation manager, VSP and design and build contractor and the client's user group prevented the team operating in an efficient and productive manner.

Case studies B and C demonstrated the scenario where the VSP was sufficiently skilled in the area of construction but was less experienced in pharmaceutical project environments.

The survey data did suggest that the validation activity should be the responsibility of both the construction and pharmaceutical groups and should be the responsibility of the whole project team and should not be left to the client (construction 63.6%, pharmaceutical 60.9%). The survey results also highlighted that construction companies are not sufficiently experienced to complete the validation of a facility i.e. writing protocols, carrying out tests and reporting outcomes, (construction 63.6%, pharmaceutical 56.5%).

10.2.3 Proposition Assessment: P3

P3: *In order to maximise the potential success of the project the validation process should be controlled through feedback and sequencing of implementation tasks.*

Thompson & McHugh (1995, p.61) acknowledge that organizational success is linked to adaptation and understanding of the client's project environment to reduce uncertainty. Culture clashes between groups occurred in case A and caused some uncertainty within the project environment.

The cybernetic validation model acts as an open system because it engages in interchanges with the environment. Environmental intrusions alter the system and force structural change or adaptation. This was clearly demonstrated in case A, where the party initially responsible for providing project validation withdrew from the task environment.

Feedback

In achieving the desired output of regulatory compliance the goal-seeking complex system contained limited sensory apparatus to distinguish deviations between process outputs and goal-states. This was highlighted, in case C, where the design review sub-process was not implemented by the project group and critical GMP items were omitted. The errors were observed as output mismatch information and were returned through negative feed back. Control action was taken at the system directing center to reduce the deviation from the output goal.

The appearance of negative feedback within the validation process moves the system which has strayed from the goal, back to goal. Feedback systems that cause amplification in control action are termed positive feedback systems. As the positive feedback acts in the same direction as the deviation it supports the direction of movement. Unplanned intervention will result in systems becoming unstable and uncontrollable and would be undesirable when goal seeking.
A degree of positive feedback was demonstrated by the selection of an inappropriate air conditioning system in Case Study C which did not receive adequate quality review early in the program. The result was that following case study C a corrective action plan was drafted to modify the newly installed HVAC systems.
This scenario displayed an element of positive feedback control whereby system deviation from its goal state increased until a critical point was reached.

Lag

The effectiveness of control is at a maximum when the time lag between the corrective action and the process output is at a minimum. Control action was influenced by the structure of the task organization and the reporting time period. System structure within the client's complex hierarchies meant that information flow was restricted and communications were slow from one function to the next.

10.2.4 Proposition Assessment: P4

P4: *The complexity of the validation testing procedures should be appropriate to the complexity of the systems in the task environment.*

The study data suggests that the pharmaceutical project environment is one that has high levels of complexity. All cases exhibited high levels of observed building system complexity, process system complexity or control or organizational complexity, as was noted in case B. Case A demonstrated that validation test procedures were not appropriate for the installed building systems. The survey data only partly backed up proposition P4 and as previously noted during observation of the validation process, complex systems do not necessarily require more complex or elaborate testing than simpler systems. If a risk based approach is adopted and critical items are examined the level of validation testing may be smaller than initially believed.

10.2.5 Proposition Assessment: P5

P5: *The desired system output, that of regulatory compliance, is affected by differing views of quality.*

This proposition proved the most difficult to test. Although the survey supported that there were differing views of the characteristics of each industry, it did not offer support to the proposition that the views influence project success.

The survey highlighted cultural differences between groups. The pharmaceutical industry is viewed as technological, inflexible, highly regulated and committed to research and development. The construction industry is perceived as highly contractual, with low implementation of technology and research and development. Generally, the survey indicated that the pharmaceutical working environment was less stressful than the construction industry environment, provided good training opportunities and had higher levels of motivation than in the construction industry. Construction respondents also viewed pharmaceutical facilities as complex and survey data did demonstrate that there were differences in understanding of regulatory compliance and quality. The construction industry responses indicate a moderate level of understanding of quality practices in the task environment whereas the pharmaceutical industry responses highlight a higher level understanding of the validation process.

As noted by Godfrey (2001) understanding of the meaning of the term quality is based around defining it for a specific service or product and the service provider must be focused on the product-service chain of the industry which is served.

The construction industry's traditional view of quality is rooted in the workmanship of the finished product. If the final building is constructed to high quality levels it is less important to measure quality at process stages. Pharmaceutical quality has been shown through this research as being almost the opposite where product quality is built in and continually tested throughout the transformation phase.
The sensitizing interviews indicated that construction testing is typically carried out at one stage of the project; in the commissioning phase and was noted as the phase 'everything gets tagged onto'. This contrasts with 'checking' processes undertaken in each of the case studies which were time series dependant and continued throughout the projects. This difference between the groups definition of quality may be a significant reason why projects of this type under achieve.

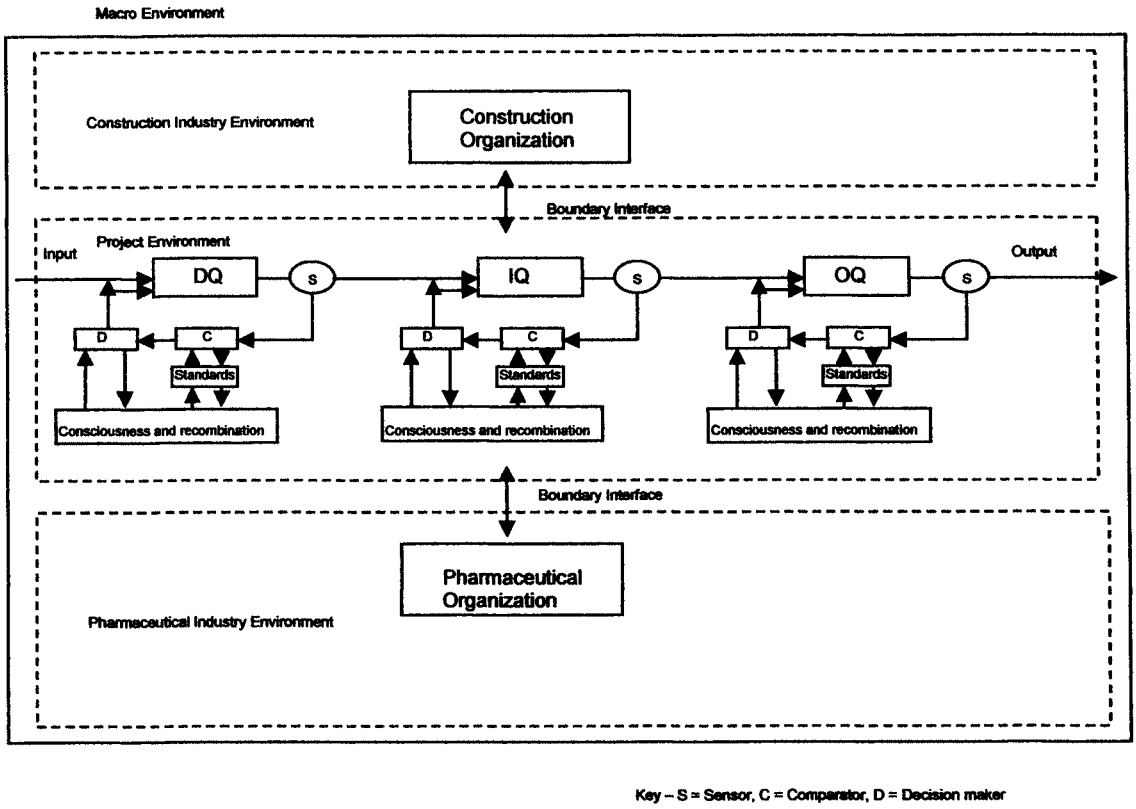
10.3.0 Revisions to the model

10.3.1 Original Model

A cybernetic model of the validation process was proposed in chapter four. It is now possible to evaluate the model and determine if the data has modified the model in any way.

The original model is shown in figure 10.2 below.

Figure 10.2: Originally proposed Cybernetic Validation Model



When the model was assessed by comparison with fieldwork and survey data, the following differences were noticed:

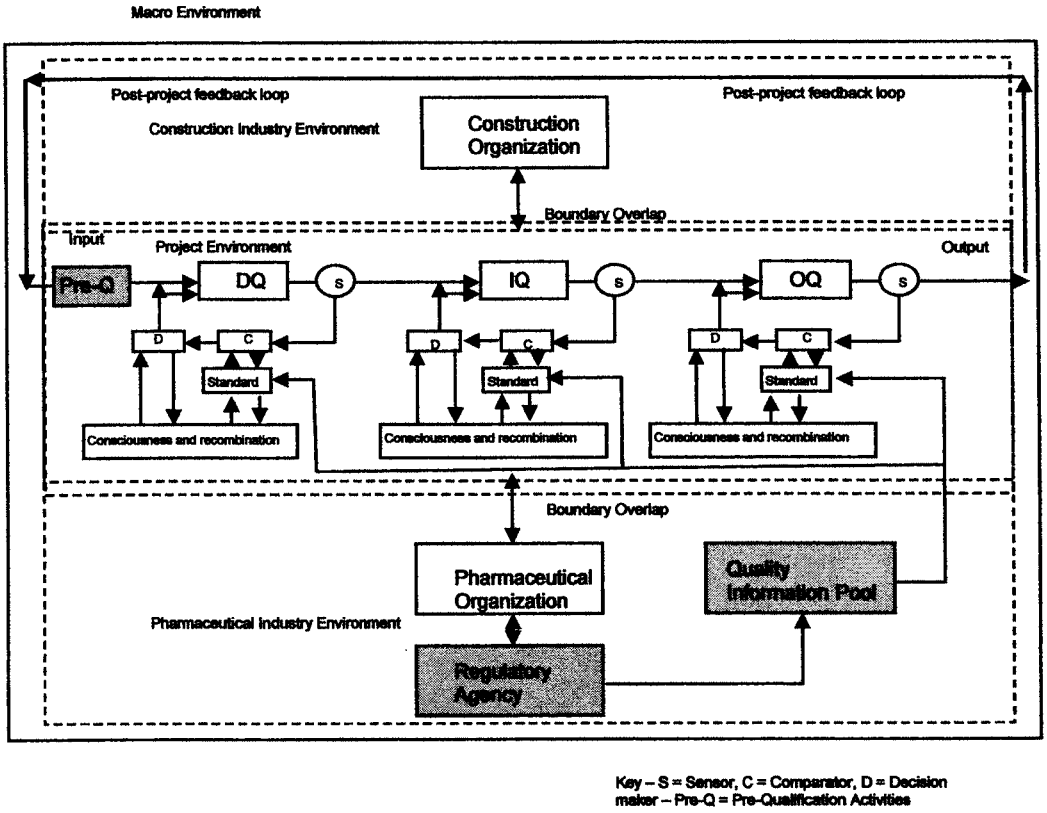
1. System control was significantly influenced by the availability of regulatory information which existed mainly in the pharmaceutical environment[1].
2. The boundary interfaces separating each environment moved and overlapped to form the project environment[2].
3. The pre-qualification activities (Pre-Q) were more influential than initially considered[3].

[1] See section 9.4.3, 9.4.8 and 8.10.
[2] See section 8.10.
[3] See sections 8.9.1, 8.9.2 and 8.9.3.

10.3.2 Modified Model

Empirical analysis of data presented in Chapters Six, Seven, Eight and Nine and discussions in this chapter has enabled construction of a revised model. The model is constructed from the results of correlations, pattern matching and observation. Matko *et al,* (1992, p.8) recommend that dynamic models should be simplified representations which contain only essential aspects of the system. In line with this, the problematic themes relating to culture, attitude, planning, implementation, system complexity and quality and regulatory compliance are omitted for clarity. The grey shaded boxes of the revised model indicate the changes from the original position derived from the literature. The new findings of pre-qualification activities, overlapping and shifting project boundaries and the significance of the position of the regulatory information pool have shaped the model's form. The model also has had a post-project feedback loop added. This feedback loop represents the final process steering mechanism which would be implemented in the case of failure occurring outside of the project domain and represents the 'worst case' post-project remedial action that might occur following unsuccessful regulatory inspection.

Figure 10.3: Revised Cybernetic Validation Model



10.4 Summary of research findings and contribution

The main aim of the research was to bridge the knowledge gap to explain the reasons why the validation of building systems in pharmaceutical facilities often fails to achieve its objectives. To achieve this, a basic analytical classification model was constructed to provide an initial framework. The model was then revised to show the relationships between the important system entities. The models original propositions were that the system output, that of a compliant facility, was influenced by two main observable themes; understanding of implicit regulations and implementation through system control.

The model was assessed using sets of qualitative and quantitative data from three construction projects and an industry survey. The primary data, from the fieldwork case study projects, was analyzed using interpretivist techniques namely, grounded theory and participant observation. It is acknowledged that methods of this type have received criticisms and theories derived from qualitative data are said to be impressionistic. The research has been undertaken with this very much in mind and

has provided a systematic and rigorous description of how theory is generated and how it is relevant. This has been done by constructing a data set collection model[4] and providing qualitative evidence which has been cross referenced within the discussion of the fieldwork as a way of increasing the validity of the methodology. An industry survey, which canvassed the views of both constructor and client, was also undertaken to build on the studies validity by providing a degree of external validity. This mixed mode research strategy has been successfully practiced by researchers such as Pare (2001), in his research into information systems, where he used both exploratory (theory building) and explanatory (theory testing) techniques.

The review of the current state of knowledge about quality systems and validation of pharmaceutical facilities in chapters two and three highlighted a number of key issues.

Firstly quality is notoriously difficult to define and its definition can be shaped by its use. The application of quality techniques to both the construction and pharmaceutical manufacturing industries were found to be very different in their approach and in the case of validation, in its language of implementation. One definition of quality 'conformance to requirements' by Crosby (1980) was found to be inadequate as an indicator of quality in facility validation because it does not include process quality and the ideals of a total quality system. The study highlighted that there was a general lack of understanding and communication of client requirements because of limited early involvement between both groups.

The research showed that the literature on facility validation is almost exclusively produced by the healthcare technology industry and writers such as Allan (2004) and Bender (1996) have noted that facility validation is costly and time-consuming. This also underlined the general view of the construction industry that the validation process is not widely understood outside the environment of pharmaceutical manufacture and is viewed with some negativity. Differing views of the meaning of quality were identified. Traditionally manufacturing based quality was concerned with the final product whereas construction quality was viewed as levels of workmanship. The study was in agreement with the existence of both these traditional differing views of quality.

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[4] See section 5.6.

Chapter three identified that the validation process was represented as a sequential set of interconnected activities. The research found that the pre-qualification procedures were of greatest importance as they confirmed existence of GMP in the facility design prior to commencement of construction. The research in chapter four noted that system control is most efficiently achieved through cybernetic goal-seeking processes.

It was indicated by the research that the validation transformation process deviated from the control model. In assessing the validity of the cybernetic model, the concept of bounded rationality cannot be ignored because, according to Simon (1957), 'when people make decisions they are often faced with complex choices and are often unable to make objectively rational decisions'. The reasons for these cognitive and knowledge limitations are, that it is impossible to (1) generate all feasible alternatives to a choice, (2) obtain and transform all the data into a form that allows prediction of a given alternative, and (3) value the expected consequences accurately and choose among them. The quantity of information required to monitor and coordinate control actions and the large number of feasible options available are suggested by Morecroft (1985), as important factors that add to the complexity of decision choices. The research highlighted that location of this information pool is in the pharmaceutical domain remote from the construction environment.

The main aim of the study was to examine why the validation activity often fails to meet its objectives by constructing a model of the validation of pharmaceutical facilities. The research findings support the initial propositions that the desired system output of regulatory compliance is affected by the understanding of implicit regulations and implementation through system control. *Structural correspondence* can be said to exist between the data and the model. Direct relationships between the data and the model suggest that it has been proved, in the reality of the perceived phenomenon (the validation process), that the model may exist and can be used to make predictions about how the 'real world' reacts to system changes.

It is believed that the study of the complex under-researched area has contributed to the understanding of the validation process.

10.4.1 Limitations of the Study

The research contained some limitations which were as follows:

The selection of the case study projects has enforced a number of restrictions on the research study. The first restriction of the study is related to methodological techniques. Participant observation and grounded theory techniques required note taking and memoing to be undertaken on a regular basis. The difficulty in compiling observation notes that are produced straight after some important event resulted in what Shwartz & Schwartz (1969, p.89) have noted as retrospective observation. The documentation of events sometime after they occur is a retrospective process of recreation and analysis which can affect the accuracy of an observation.

Case study data collection is, as Yin (1994, p.55) notes, not routinized as in experimental or survey research and the skills required to carry out such research are generally learned in the field. Therefore at the outset of the fieldwork skill levels were low but throughout the data collection phase the basic skills of adaptation, listening and asking questions increased.

Early in the study it proved difficult to define operational measures for demonstrating change as set out in the study objectives. Only after the model development and addressing specific case study techniques such as multiple data sets was it possible to progress the empirical enquiry. This caused an obvious mismatch in some of the data collected by the industry survey and the fieldwork study.

Large quantities of documentary information were collected during the fieldwork period. It is accepted that this type of data has been critical in the study but it is also acknowledged that single pieces of documentation can be edited and shaped by the writer. For this reason the data were only used to corroborate and augment actual observations and events that were observed by the case study researcher.

The revised cybernetic model has use limitations. As all of the analytical data used to develop the model was derived from pharmaceutical facility construction projects, the application of the model in similar task environments such as the petro-chemical, computer or healthcare industries would require additional research to evaluate relevance. Those industries mentioned have similar characteristics to those of

pharmaceutical manufacture and might benefit from increased control procedures to limit project non-conformances.

It was noted earlier[5], in Chapter Two, that pharmaceutical manufacturing equipment and systems also require validation prior to use. The findings of this study may also be transferable to equipment and certain automated systems employed in everyday pharmaceutical manufacture. For example, if a building is classed as a 'housing' for manufacture the same could be said for a climate controlled stability suite or industrial refrigerator. The sequential validation steps of specification, design, installation and operation would be similar to those used in facility validation. An essential difference between equipment and facility validation is that in general single pieces of equipment have one manufacturer whilst buildings require input from a large range of professions, trades and suppliers and therefore present more complex project management problems.

It is acknowledged that external 'noise' factors such as market conditions and political environment could affect the use of the model. For the duration of the research study there were no significant legislation changes or factors that impacted on the development and validation of the model in the UK. However, if the study had been implemented in another geographical region or at a different time, outcomes may have been quite different. As noted by Tang & Ogunlana (2003, p.127), 'the impact of the economy on an organizations' performance is influenced by the organizations' systemic behaviour'. The response to 'external' change would therefore be dependant on the magnitude of change in the operating environment and the organizations' internal operating systems.

10.4.2 Reflections on Learning

This postgraduate research study represents the researcher's avid interest into an area of 'warm' research activity that has largely received little or no research coverage. The research problem straddles two very different disciplines and this may be one of the main reasons why the subject problem has not been widely reported in the mainstream academic press.

[5] See section 2.6.

The study has built upon previous industry experience and on a master's degree dissertation. It has benefited from having accessible sources of data collected during the writers work based activities throughout the period of this Phd.

During the study period considerable experience has been gained in making critical use of published work from the existing body of knowledge that surrounds the topic. Through self study and university based training courses there has been the opportunity to experiment with various ethnographic tools for data collection and analysis and software packages such as SPSS.
Whilst the work at times has been solitary and difficult, it has been rewarding and has provided a platform on which to build in both future academic and non-academic endeavours.

10.4.3 Recommendations for Further Research

The new cybernetic model of the validation process would benefit by being validated against further case studies of differing facility types such as biotechnology, bulk manufacturing and sterile facilities. This should be done by limiting the research variables in order to examine the impact that different facility types have on the validation process. It was noted in chapter three that sharing of cost data between both parent industries was uncommon and the validation process was under researched. Further studies would benefit both industries in providing an understanding of the process of planning in relation to organizing resources, budgets and schedules.

The study of the effect of emergent problematic themes on the validation process is complex and time consuming. One of the methodological constraints of the study was the extended period of site based data collection and analysis. Further model assessment could be undertaken by analysing model sub-processes, such as Pre–Q, DQ, IQ or OQ, in projects that are at different life-cycle stages. By doing so this may generate data of a greater depth over a reduced fieldwork period.

Further studies of the implementation of validation methodology as a life-cycle checking process, instead of the more traditional commissioning checks at final stages of the construction process, in non-healthcare and drug manufacturing buildings could be carried out. This would provide valuable sources of information which would likely benefit different sectors.

ABSTRACT

The construction, commissioning and hand-over of pharmaceutical manufacturing buildings have become increasingly controlled by the requirements of regulatory agencies. Legislation requires that the process of *validation* is undertaken to establish that the facility is constructed in-line with the principles of pharmaceutical *Good Manufacturing Practice* (GMP).

The validation process acts to ensure that the construction and building services systems are designed, installed and operate as intended and do not affect the quality of the manufactured product.

A central objective of this thesis is to examine the sequential validation process and influencing factors that contribute to the facility attaining agency approval.

A comprehensive review of the available literature indicates that projects regularly fail to meet their regulatory objectives due to the building provider and client's differing understanding and views of the validation process and of GMP.

From this literature a validation model is derived and proposes that the design, installation and operation stages of the validation activity are time-series dependant sub-processes controlled through sensing, feedback and comparison.

The research was largely qualitative, case-study based and used an interpretivist approach to analysis, which relied on participant observation and grounded theory techniques. Additional, external validation of the model was sought by collecting and analysing empirical data from an industry questionnaire.

The results of the study demonstrate that significant deviations between the model and the data exist and measures to construct compliant pharmaceutical buildings are often underdeveloped and result in unsuccessful project outcomes.

The criteria by which the success of any construction project is judged are normally time, cost and quality. Time and cost are readily measurable, but the meaning of quality, in relation to the validation activity, can be more elusive and this is at the root of the problem of successful validation of pharmaceutical buildings.

UNIVERSITY OF NORTHUMBRIA

THE VALIDATION OF PHARMACEUTICAL BUILDINGS

By

Neil Render

A thesis submitted as partial fulfilment of the requirements for the degree of

Doctor of Philosophy

Department of the Built Environment

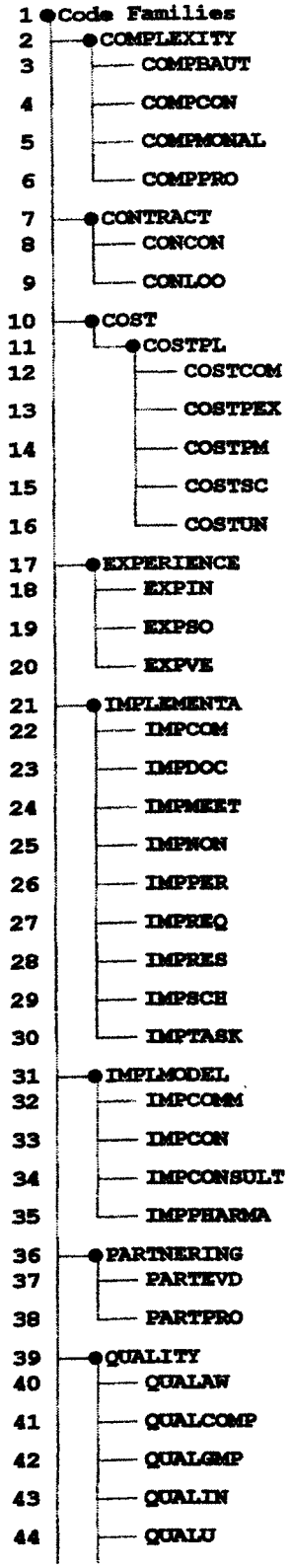
March 2006

VOLUME TWO

VOLUME TWO - APPENDICES

APPENDIX A

No.	Question	Reason for asking
1	What are the main reasons for the xxxx project?	Primary Decisions?/system boundary.
	At which stage in the project did the validation activity start?	Is the activity addressed at the correct time?
2	Who is responsible for and who is involve in the validation activity?	Establish the make-up of the team
3	At what stage in the project was facility validation considered?	Is the validation activity considered at the correct time?
4	Who was involved at project inception, design, installation, commissioning?	Who was responsible for the major validation/compliance decisions
5	What was the main scope of the validation activity?	What specific facility items are tested? Any GMP critical items missed?
6	How was the duration of the validation activity calculated?	Identification of duration calculation methods?
	(If a rule of thumb method used - What's the basis of method?	
7	How was the cost of the validation activity calculated?	Identification of cost calculation methods?
	(If a rule of thumb method used - What's the basis of method?	
8	What level of compliance is to be achieved - FDA or MCA?	A measure of actual compliance againts regulations
9	Do you Know why?	Indication of which geographic area in which product is to be sold.
10	Has the validation activity had any effect on you in terms of procurement method?	How is the validation activity addressed in the contract.
11	Is some form of partnering being used between any of the groups?	Advantages/disadvantages of partnering? Effect on validation?
12	Do you think the project is/was sufficiently resourced? In terms of construction/engineering/validation etc?	Description of any resourcing problems that may effect validation
13	What previous experience do the validation team have?	Are those with insufficient experience involved? Effect on outcome?
14	What events or issues were relevant to the project outcome?	To identify general problems that may be of significance.
15	Any group not performing? Any group performing extremely well?	To identify specific problems that may be of significance.
16	Has the validation activity had any effect on you in terms of planning?	Is the validation activity seen as a neccessary evil? Identification of problems?
17	Has the validation activity had any effect on you in terms of implementation?	Identification of problems?
18	Was there/is there any pressure or great urgency placed upon you to complete the project and get on with the next?	Is there sufficient validation works or is it an after thought?
19	How much importance is placed on the validation activity in relation to the project as a whole?	Is the activity sufficiently addressed?
20	Sufficient site meetings and opportunities to review progress?	Is a structure in place for successful documentation production and execution.
21	Was a GMP audit carried out? Who by?	Any initial review?
22	How are the clients requirements established and communicated?	Communication problems?
23	Can you describe an instance when the validation helped in overall project implementation	Highlight advantages
24	Can you describe an instance when the validation hindered overall project implementation	Highlight disadvantages
25	Where are resources located?	Has geographical location have any effect?
26	Where do activities and events happen? Geographical factors – are decisions made remotely to the project site?	Has geographical location have any effect?
27	During the project was there any significant changes to the facility? (Change control/variations)	How are variations delt with? How are changes reflected in quality documents?
28	How were these changes accommodated in the validation documentation/testing?	How are variations delt with? How are changes reflected in quality documents?
29	Did the validation service provider seem to fully understand the clients requirements? (GMP)	Do those involved in providing the service fully understand what is required?
30	Did the client seem to know what was required in terms of GMP.	Is the client aware of what is required?
31	Where commissioning contractors used to assist in validation of the facility and equipment?	Streamling validation. How can things be improved?
32	How did their contribution effect the completion of the works?	Pro's and con's of implementation models?
33	Could the validation works be carried out as part of commissioning?	Streamling validation. How can things be improved?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3 COMPBAUT
4 COMPCON
5 COMPMONAL
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7 CONTRACT
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12 COSTCOM
13 COSTPEX
14 COSTPM
15 COSTSC
16 COSTUN
17 EXPERIENCE
18 EXPIN
19 EXPSO
20 EXPVE
21 IMPLEMENTA
22 IMPCOM
23 IMPDOC
24 IMPMEET
25 IMPMON
26 IMPPER
27 IMPREQ
28 IMPRES
29 IMPSCH
30 IMPTASK
31 IMPLMODEL
32 IMPCOMM
33 IMPCON
34 IMPCONSULT
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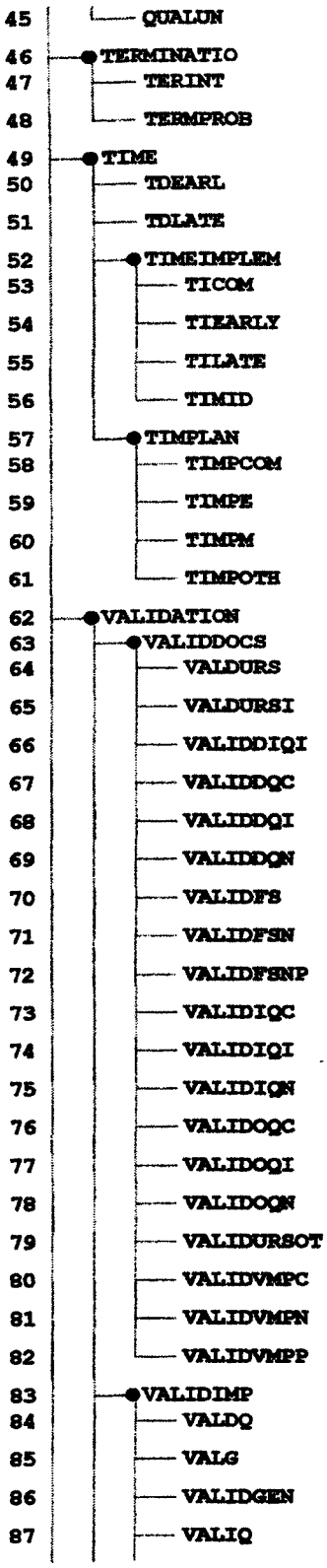
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78 VALIDOQN
79 VALIDURSOT
80 VALIDVMPC
81 VALIDVMPN
82 VALIDVMPP
83 VALIDIMP
84 VALDQ
85 VALG
86 VALIDGEN
87 VALIQ

88 └── VALOQ

	Code Word	Parent	Text	Level	Added	Modified
2	COMPLEXITY	None		2	28/06/05	00/00/00
	Project Complexity - complex plant/equipment/facility					
3	COMPBAUT	COMPLEXITY		3	28/06/05	00/00/00
	Complex building with automated technologies					
4	COMPCON	COMPLEXITY		3	28/06/05	00/00/00
	Complex construction					
5	COMPMONAL	COMPLEXITY		3	28/06/05	00/00/00
	Complex monitoring/alarm systems					
6	COMPPRO	COMPLEXITY		3	28/06/05	00/00/00
	Complex manufacturing process interface					
7	CONTRACT	None		2	28/06/05	00/00/00
	Contractual arrangement of project					
8	CONCON	CONTRACT		3	28/06/05	00/00/00
	Contract is based on quotation					
9	CONLOO	CONTRACT		3	28/06/05	00/00/00
	Loose contractual format					
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	Validation cost planning					
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	Cost based on commissioning time period					
13	COSTPEX	COSTPL		4	28/06/05	00/00/00
	Cost based on experience					
14	COSTPM	COSTPL		4	28/06/05	00/00/00
	Based on planning matrix					
15	COSTSC	COSTPL		4	28/06/05	29/06/05
	COST BASED ON SUB-CONTRACT					

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	Inexperienced - of pharmaceutical projects				
19	EXPSO	EXPERIENCE	3	28/06/05	00/00/00
	Some experience - of pharmaceutical projects				
20	EXPVE	EXPERIENCE	3	28/06/05	00/00/00
	Very experienced - pharmaceutical projects				
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	Implementation characteristics				
22	IMPCOM	IMPLEMENTA	3	28/06/05	00/00/00
	General communications problems				
23	IMPDOC	IMPLEMENTA	3	28/06/05	00/00/00
	Specific test documentation problems				
24	IMPMEET	IMPLEMENTA	3	28/06/05	00/00/00
	Problems associated with communications - meetings				
25	IMPMON	IMPLEMENTA	3	28/06/05	00/00/00
	None attendance of task groups				
26	IMPPER	IMPLEMENTA	3	28/06/05	00/00/00
	Quality of implementation personnel				
27	IMPREQ	IMPLEMENTA	3	28/06/05	00/00/00
	Difficulties understanding requirements				
28	IMPRES	IMPLEMENTA	3	28/06/05	00/00/00
	Too few resources				
29	IMPSCH	IMPLEMENTA	3	28/06/05	00/00/00
	Implementation schedule problems				

30	IMPTASK	IMPLEMENTA	3	28/06/05	00/00/00
	Problems of task implementation				
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	Validation service provider model				
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	Commissiong group is VSP				
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	Main contractor is VSP				
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	Consultant is VSP				
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	Pharmaceutical organization is VSP				
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	Partnering				
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	Evidence of partnering				
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	Partnering issues				
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40	QUALAW	QUALITY	3	28/06/05	00/00/00
	General apprciation of quality objectives				
41	QUALCOMP	QUALITY	3	28/06/05	00/00/00
	Quality - aware of specific compliance regulations				
42	QUALGMP	QUALITY	3	28/06/05	00/00/00
	Quality-aware of specific GMP issues				
43	QUALIN	QUALITY	3	28/06/05	00/00/00
	General interest shown in quality pracices				

44	QUALU	QUALITY	3	28/06/05	00/00/00
	Quality uninterested - limited interest in quality practices				
45	QUALUN	QUALITY	3	28/06/05	00/00/00
	Quality Unaware				
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	Termination project phase				
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	Integrated termination				
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	Termination problem				
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	Time - schedule/prog.				
50	TDEARL	TIME	3	28/06/05	00/00/00
	Time - Design Stage - validation activities considered at design stage.				
51	TDLATE	TIME	3	28/06/05	00/00/00
	TIME - Design Stage- validation activities considerd at a late design stage.				
52	TIMEIMPLEM	TIME	3	28/06/05	00/00/00
	Time of implementation				
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	Early implementation of validation				
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	Late validation implementation				

	Code Word	Parent	Text	Level	Added	Modified
56	TIMID	TIMEIMPLEM		4	28/06/05	00/00/00
	Mid stage implementation of validation					
57	TIMPLAN	TIME		3	28/06/05	00/00/00
	Planning of time/cost of validation					
58	TIMPCOM	TIMPLAN		4	28/06/05	00/00/00
	Validation based on commissioning phase					
59	TIMPE	TIMPLAN		4	28/06/05	00/00/00
	Validation planned on experience					
60	TIMPM	TIMPLAN		4	28/06/05	00/00/00
	Planning matrix used					
61	TIMPOTH	TIMPLAN		4	28/06/05	00/00/00
	Validation based on other methods					
62	VALIDATION	None		2	28/06/05	00/00/00
	Validation specific data					
63	VALIDDOCS	VALIDATION		3	28/06/05	00/00/00
	Specific documentation issues					
64	VALDURS	VALIDDOCS		4	28/06/05	00/00/00
	URS not produced					
65	VALDURSI	VALIDDOCS		4	28/06/05	00/00/00
	URS produced at incorrect time					
66	VALIDDIQI	VALIDDOCS		4	28/06/05	00/00/00
67	VALIDDQC	VALIDDOCS		4	28/06/05	00/00/00
	DQ content issues					
68	VALIDDQI	VALIDDOCS		4	28/06/05	00/00/00
	DQ produced at incorrect time					
69	VALIDDQN	VALIDDOCS		4	28/06/05	00/00/00
	DQ not produced					

70 VALIDFS	VALIDDOCS	4	28/06/05	00/00/00
Functional specification issues				
71 VALIDFSN	VALIDDOCS	4	28/06/05	00/00/00
FS not produced				
72 VALIDFSNP	VALIDDOCS	4	28/06/05	00/00/00
No functional specification				
73 VALIDIQC	VALIDDOCS	4	28/06/05	00/00/00
IQ content issues				
74 VALIDIQI	VALIDDOCS	4	28/06/05	00/00/00
IQ produced at incorrect time				
75 VALIDIQN	VALIDDOCS	4	28/06/05	00/00/00
No IQ				
76 VALIDOQC	VALIDDOCS	4	28/06/05	00/00/00
OQ content issues				
77 VALIDOQI	VALIDDOCS	4	28/06/05	00/00/00
OQ produced at incorrect project phase				
78 VALIDOQN	VALIDDOCS	4	28/06/05	00/00/00
OQ not produced				
79 VALIDURSOT	VALIDDOCS	4	28/06/05	00/00/00
urs other problems				
80 VALIDVMPC	VALIDDOCS	4	28/06/05	00/00/00
VMP content issues				
81 VALIDVMPN	VALIDDOCS	4	28/06/05	00/00/00
No VMP				
82 VALIDVMPP	VALIDDOCS	4	28/06/05	00/00/00
VMP produced at incorrect phase of project				

	Code Word	Parent	Text	Level	Added	Modified
83	VALIDIMP	VALIDATION		3	28/06/05	00/00/00
	Implementation of validation activities					
84	VALDQ	VALIDIMP		4	28/06/05	00/00/00
	DQ implementation issues					
85	VALG	VALIDIMP		4	28/06/05	00/00/00
	General issue - requiring further memo					
86	VALIDGEN	VALIDIMP		4	28/06/05	00/00/00
	General issue - requiring further memo					
87	VALIQ	VALIDIMP		4	28/06/05	00/00/00
	Specific issues at IQ stage					
88	VALOQ	VALIDIMP		4	28/06/05	00/00/00
	OQ implementation issues					

```
!-COMPBAUT
                                                    !

  Critical Activities Memo                    4

  Memo - from validation manager              6
  (client) to building user manager and       7
  engineering director (both client).         8
  16-Jun-00 General note indicating the       9
  problems of the client carrying out        10
  validation works I.e lack of               11
#-EXPIN
  experience and at this stage detailed      12  -#
  documentation to allow time estimates      13   |
  and also the complexity of IQ              14  -#
  execution.                                 15

  Estimate time for validation of the        17
  facility - 98 days.                        18


  Issues                                     21


  Ductwork contractor understood that        24
  all installation would be complete by      25
  mid september.(S&G) 19-Jul-00              26

  Duration of the validation works are       28
  based on the overall project schedule      29
#-TICOM
  and made to fit, even if  19-Jul-00        30  -#
  into the final stages - C1.                31   |
                                                  |
                                                 -#

  Client states durations of validation      34
  activities appear too short.               35
#-IMPRES      #-IMPSCH      #-EXPIN
  10-Jul-00(rumor client to execute          36  -#
  documents as a cost saving measure)?       37  -#


  Basic shell erected  - holes to be cut     40
  in slabs when product transfer chutes      41
  finalized. 10-Jul-00                       42


  AHU factory acceptance test (FAT) -        45
  air leakage checks , general quality       46
!-TIMEIMPLEM
  /engineering checks. 10-Jul-00             47 !
  Engineering manager  - unclear of          48
  'project organization'. No brief for       49
  FAT, no design spec. for comparison!       50

  AHU manufacturer was asked to provide      52
  materials of construction details for      53
  his equipment.                             54

  Incorrect information received? Vendor     56
  unclear of pharmaceutical                  57
#-QUALUN
  requirements?                              58  -#
                                                  |
  AHU'S delivered to site  13-Jul-00         60  -#


  IQ documents received by client1 for       64
  comment.(see separate sheet).              65
#-VALIDIQC    #-TIME
```

```
IQ documents received by client1 for      64
comment.(see separate sheet).             65
#-VALIDIQC   #-TIME
29-Jul-00                                 66  -#
                                                |
Client considering 'in house'             68  -#
completion of validation works.           69
01-Aug-00                                 70

Client review of IQ documents - Client    72
unhappy with content. 12-Sep-00           73
#-VALIDDQI
Service provider considers they are       74  -#
complete and suitable.                    75   |
                                               |
                                              -#


Meeting client(engineering &              79
construction PM) / service provider/      80
3rd party validation consultant           81
20-Sep-00 and client validation           82
section.                                  83

Presentation by service provider          85
(C1/VSP1) of validation activities and    86
final documents.                          87

Very unclear of what documentation        89
constitutes validation I.e flushing of    90
#-EXPIN
pipework.                                 91  -#
                                                |
pressure testing etc.                     93  -#


C1 1 decides to complete documents.       97
Sep-00                                    98
```

Case Study A
Interview with G W - Contractor 1
Project Manager. 020501

Key: C1 - Main Contractor 1, C11 -
Client 1, Comm 1 - Commissioning
Organization.

Question 1

N.R - At what stage of the project was validation considered,when did you get involved in the project?

G.W - We knew of it, we knew that some
#-CONLOO
form of validation input would be -#
needed. The difficulty I think was -#
getting an appreciation to what extent
!-QUALIN
we would be involved. We had our own !
idea. A lot of time with contractors
its what you can get away without
doing. So we were quite happy to sit
#-IMPTASK
back and hopefully do the bare minimum -#
although it never turns out that -#
!-VALG
way. But I think it was fair to say !
that we were there to provide a fair
bit of input.

NR - I find a lot of people provide an enhanced commissioning and its not really clear what people require for validation.

GW - Very, very true.

NR - I' ve seen that before.

Question 2

NR - Who was involved initially in the project?

GW - I think even at the stage when VSP1 were known as VSP1 they had
!-IMPCON
already been bought out by C1, its !
!-PARTPRO
just that they hadn't had the !
launching of the new C1 logos and
everything else. So they were
actually C1 Clean Room Group..C1
Process. But they were ultimately
working for C1 under C1 banner and
they were involved from day one,
they in fact headed up the design
really and used the M&E services as
just a spin off really , with the
information just going backwards and
forwards

Question 3

NR - What was the main scope of the validation activity?

#-QUALAW -#

GW - It was the clean rooms and the process equipment. That was the primary validation function , wasn't it overall. People forget the M&E services and people like to think that #-VALIQ #-VALOQ there is not as much to do on M&E services, but it still gets very involved. -#

Question 4

NR - How was the duration of the validation activity calculated? Did someone sit down and decide it was going to take x number of days or was #-TIMPE it a case of 'we've got this slot here can we get these people in to come along and do it then or was it something that you were unaware of ? -#

GW - I think in fairness from the M&E services side, Peter and myself and Mike who was ultimately project manager were aware that I would be involved in the validation at whatever point in time my services would be needed to drop into that slot, so at any point in time I would cover that element of the work. Yes I think we were aware and made due allowance.

NR - What was the duration based on, was it based on the duration of the commissioning?

G.W. - Yes, very much so we knew we !-COSTCOM would have a certain element of ! !-TDLATE forward planning as regards orders for ! equipment procurement of equipment and the tagging and things like that and the traceability of the products. We envisaged it would !-COSTPEX #-TIMPCOM become a lot more involved around !-# commissioning stage, that what | everything gets tagged onto,really. -#

NR - Were you involved in the cost of that as well?

G.W - I wasn't as such, I think ultimately the time built in for me to be on the job would have included the validation, I don't think that a specific cost was set aside for a specific individual. I think my time in fairness was not fully occupied five days a week on the project so any sort of validation time would be taken up by that.

Question 5

N.R - Do you know what level of compliance the design and GMP installation aimed for do you know if FDA or MCA , were you involved in that side of things or would that have been VSP1?

G.W. - It would have probably been
!-IMPREQ
VSP1's package. No the only sort of approvals we were working towards or standards were the actual clean room standard that we had to achieve,
!-QUALOW
which was pretty unknown.

NR - The functional specification the
!-VALIDFS
very first document didn't state what levels to be achieved.

G.W - That's right

N.R -I think a design was put together that provided a general level of acceptance for this level of clean room , and then it was down to Cll to test check that it did comply to MCA or FDA regulations. With the level of filtration in there, the HEPA's I think it surpassed any levels, I
!-IMPCOM
think someone probably made that decision early on to make sure that it complied.

G.W - I would imagine they would have done.

Question 6

N.R - Did the validation have any effect on you in terms of procurement method? What sort of contract were you working on ?

!-CONTRACT
G.W -It was design and build.

N.R - Was there anything in the contract that mentioned validation?

!-COMLOO
G.W - No, we were just given a design brief to work against that ties you to performance figures for each piece of equipment we had to purchase, but other than that no.

Question 7

N.R - Was there some sort of partnering used between yourselves and anybody else?

!-PARTEVD
G.W - Yes, we would always use a commissioning specialist Comml,

there is no in house capability for commissioning engineers, but very rarely probably up until now has it been in a partnering situation, its normally a straight forward sub-contractor basis. But more and more now we are looking at using commissioning management, rather than just straight forward rather than just air and water balancing technicians supervised by the site engineer. We tend to look for the commissioning package to be the whole thing.

NR - Was there any contractual link between C1 and Comm 1 on the project?

G.W - they were sub-contracted to us to do the commissioning on the project and on other projects and would be expected to fulfil there contractual obligations and if not they would not get the next contract.

Question 8

NR - Do you think that the project was adequately resourced ?

G.W - Construction companies tend to keep jobs lean, but I thought it was reasonable. I think it would be difficult to add many more people into the system. The main problem was getting an appreciation for what needed to be done and the time scale, a realistic time scale for doing it. I think once that was established I think it worked well, it worked fairly well. We could have possibly could have done with another guy doing a bit running around really as an intermediate just chasing people up and pulling them together, but in fairness we did have a commissioning manager so that did help. I think without that it would have been a problem.

Question 9

NR - What experience did the validation team have?

GW - I think they will be quite familiar , I would imagine with most of the aspects of validation that they would have come up against on the process side. Like I mentioned before the M&E services it tends to be a bit more of an enhanced commissioning activity were we just try and enhance our documentation to satisfy in this case C11's validation teams needs. The problem would have been if C1 had been asked

to produce the validation documentation. I think we are quite capable of filling in other peoples but actually to produce the protocols from the outset would have been a different story. I think that would have been a problem.

Question 10

NR - Was there any main events or issues that were relevant to the project outcome?

GW - I think the biggest problem or two of the biggest problems was

#-EXPIN
initially the clients understanding of what he wanted because it seemed to be a moving target for quite a long time. In fairness you have to sympathize with because it was a pilot plant and inevitably there is going to be hiccups when you are doing that, as things are being built things become glaringly obvious and they have to be attended to mid stage which obviously is a problem when you have hired contractors to do a set piece of work.

#-IMPLMODEL
I think if there had a bit more of an input from the client at an early stage things may have been resolved or things would have run smoother.

#-COMPPRO #-COMPMORAL #-COMPRAUT
Positions of equipment and if equipment is a new piece of equipment and has not been sufficiently looked into or researched then it arrives on site and all of a sudden there is ten extra electrical supplies, water supplies,mechanical supplies that are needed and its wherever you can bring them from, is there a distribution board and that sort of thing that becomes a problem. Also holes being cut in floors for equipment shoots next thing you need to be trimming structural steel. It's the knock on effect,things aren't as simple, there are so many repercussions that have to be taken into account.

Question 11

NR - Was there any group that were not performing or performing extremely well on the project?

GW - Yes, sometimes CL1 were hard

#-IMPMOM #-IMPRES
work , it was difficult to pin somebody down and when we sat down with them it we sometimes really hard to get a decision out of somebody, we had to really pin someone down make a decision. It did seem to take

#-IMPREQ
quite a long time. I think the

client also had a problem 325 |
understanding what was required. 326 -#

I didn't think the builder performed 328
well in as much that again it was hard 329
for him to, for all that they were a 330
#-IMPLEMENTA
clean room specialist, it seemed at 331 -#
times that the people on site found 332 |
it hard to grasp what needed to be 333 |
done to get the things up and 334 |
running and what were the real true 335 |
requirements of the M&E services 336 |
people and the process people. 337 |
Everything to them tended to a bit 338 |
black and white, I think they 339 |
weren't very flexible. 340 -#

Question 12 342

NR - Did the validation activity have 344
any effect on you in terms of planning 345
or implementation. Were you handed a 346
program initially from VSP1 to build 347
into your overall program? Was that 348
something that was decided early on? 349

#-IMPLEMENTA
GW - No the interface between VSP1 as 352 -#
such and the on site installation team 353 |
was pretty poor, I mean I think VSP1 354 |
tended to back off and leave 355 |
everything with C11 to sort out 356 -#
because it was a strange contract in 357
as much as VSP1 were working direct 358
#-IMPLMODEL
for C11 and didn't have an input with 359 -#
the rest of the C1 team, the site team 360 |
and we had a situation where C1 site 361 |
team as C1(Clean room group) and C1 362 |
were working also direct for the 363 |
client and the client was sat back 364 |
at that point in time thinking why 365 -#
are VSP1 just telling you what to do. 366
But in theory there was no direct 367
link there and it became a fair bit 368
confusing at times. 369

NR - So you had the client, VSP1.. 372

GW - Appointed to design the process 374
systems. 375

NR - Then you had C1.. 377

GW - Well C1(Clean Room Group) with C1 379
working direct for C1 (Clean Room 380
Group). 381

NR - As c1 worked or c1(Clean Room 383
Group)did this cause any confusion? 384

G.W - Yes, the client often wondered 386
why certain groups appeared not to be 387
talking to each other, it was a bit 388
tricky really. 389

Question 13 391

N.R. - Was there any great pressure put on yourself to get the project rapped up and get on to your next job?

G.W. - there is always pressure to get the thing rapped up, obviously not so much as you have somewhere else to go but from the point of view that the money is running out, and they could ill afford to keep me on site. But I think at the end of the day its more prudent to get the job finished and get it finished right once than coming back and do it again and again.

Question 14

N.R. - How much importance is placed on the validation activity on that particular job by C1, was it seen as important or a chore that had to be done?

G.W. - In fairness I think it was a bit of both. It can come down to individuals really, like myself I've worked on a fair few pharmaceutical projects, I like to think I've got a reasonable appreciation of what is needed in validation so I was open minded and feared the worst. It sounds an awful thing to say but I was quite prepared to be put through what we were put through as regards validation, to me that was as straight forward as you would expect from any pharmaceutical project these days, but a lot of the time it is seen as a necessary evil, a lot of people try and shy away from it, bury there head in the sand but at the end of the day it needs doing. The quicker people wise up and take the bull by the horns the better I think.

Question 15

N.R - Do you think there is sufficient site meetings and opportunity to review progress on the project with the client?

G.W - At the design stage for the brief time I was there when VSP1 were camped on site, it appeared that C11 were quite happy and sit back and in fairness they were paying for a service. There did not seem to be a great level of communication between VSP1 and C11 and the rest of the C1 group that were there and the meetings that ..when they did happen seemed to be to involved, there seemed to be a

mass of people there and nothing ever seemed to be achieved, I think that was a problem really. At times it was as if nobody could really grasp what was going on and there was no proper direction. It was a case of

#-IMPMEET

the guy who was running the project was from a construction background and maybe didn't fully understand the pharmaceutical industry and all aspects of it. In fairness all the expertise was there to do that but I think it just got lost in such heavy meetings.

#-IMPLEMENTA

If you are going to pick someone to lead it, it couldn't be anyone else I suppose the construction manager is directly or un-directly linked with everything so in theory he should have a more wider scope of the job than anybody.

N.R - Do you think that its something that will improve in the future, Once construction companies do this type of work and obviously validation is becoming a bit of a buzz word, if you don't validate it you cannot really manufacture in the plant so its something that may start popping up in contracts?

#-IMPLEMENTA

G.W - I believe that your run of the mill construction company I think will find it very difficult. I think in

#-IMPLEMENTA

situations where you have this type of project it will be more and more construction management teams that will head it up, where they have the actual facility or the quality of individual in there within there structure who can embrace everything really. Because I think that your general run of the mill construction manager wouldn't be able to grasp or wouldn't have the knowledge. Not being able to grasp is not fair, but you know the knowledge of what validation requires.

Question 16

N.R. At what stage did the validation activity start? Well you were saying at inception of the project VSP1 were involved and the on site testing was carried out in October 2000.

G.W - YES.

N.R - Can you describe an instance where validation helped overall project implementation. Where there any benefits in validating some of these systems?

#-VALIDGEN $-VALIQ
G.W - Yes, I think it helps the 525 -#-$
checking process, I think that by 526 |-$
virtue of just going through the 527 |
validation it flags things up or and 528 |
if done at the right time you know 529 |
can flag up potential problems. If you 530 -#
cannot just sort of see the wood for 531
the trees you would not pick up or not 532
pick up until it was too late and I 533
think it did help in that respect. Its 534
quite simple to go out there and do 535
run of the mill balancing, balancing 536
water and balancing air systems its 537
very straight forward, but when you 538
are talking about integrated process 539
and mechanical services systems, with 540
#-VALIQ
the way in which validation goes into 541 -#
it in more depth that problems are 542 |
found at an earlier stage, I think its 543 |
fairly useful. A prime example that 544 |
you'll know about is the filter 545 |
situation that we had were we ordered 546 |
filters that were specified, but 547 |
Barkell who supplied them delivered 548 |
the wrong filters that were 549 |
subsequently installed without 550 |
checking and the validation team came 551 |
and checked them and they were found 552 |
to be wrong so they had to be taken 553 |
out and put back in which under normal 554 |
circumstances that may not have 555 |
happen or even found out, or would 556 |
not have been important. 557 -#

Question 17 559

N.R - Can you tell me about an 561
instance where validation hindered 562
overall project implementation ? 563

#-VALIQ #-VALOQ
G,W - only by virtue of the checking 565 -#
and witnessing, in as much as its very 566 |
difficult to get the two, you set the 567 -#
commissioning team away and you've 568
only got a certain amount of time to 569
actually, or initially when you do the 570
programme and you take a 571
commissioning team on board, if you 572
don't make them aware of the time 573
scales and the fact that there is a 574
validation team on board who are 575
going to be sort of looking over 576
there shoulder it can tend to be a 577
#-TIMPLAN
bit more long and drawn out. I'm 578 -#
afraid the upshot of it is, its 579 |
understood at every stage again 580 |
what's appreciated and what validation 581 |
want then we can build that time in. 582 -#
The problem is if you don't do that 583
and its not made aware early enough 584
and it can be a problem. 585

N.R - yes, I think there was an 587
instance where the validation team 588
missed the witnessing of a filter 589

test. 590

G.W - Yeah, the commissioning team 592
will do it, you know everything will 593
seem fine, but unfortunately if they 594
have not witnessed it they will have 595
to re-witness it and of course next 596
minute you have the commissioning 597
company coming back saying I want 598
paying again for doing this because... 599
communication, organization problem. 600

Question 18 603

N.R -location of resources. C1 are 605
based in York, VSP1 Alton 606
Hampshire,C1(Clean Room Group) York, 607
sub-contractors north east based? 608

Question 19 610

N.R - During the problem where there 612
any significant changes to the 613
facility? 614

G.W - It was more of a co-ordination 616
issue really. Generally the systems 617
were the same as design perhaps the 618
LEV had a few extra outlets added. The 619
problem with co-ordination, when it 620
was realized, obviously our guys had 621
laid the M&E services design out onto 622
a drawing, and the problem arose 623
when later on in the day, quite a 624
#-VALIDGEN
bit later on in the day the 625 -#
equipment was being located and when 626 |
the connections to the equipment 627 |
were trying to be co-ordinated with 628 |
the m&e services I think the two 629 |
things 'never the twain shall meet'. 630 |
Unfortunately that meant moving 631 |
around the m&e services and 632 -#
re-design to the ductwork systems, 633
were in some cases happening after the 634
event, you know we were taking 635
ductwork out and re-hashing it which 636
that was a problem. 637

N.R - Did that have an effect on the 639
validation documents, did they have to 640
the documents? 641

G.W - I don't believe so I think it 644
was caught early enough, nothing had 645
been tested at that stage and it 646
didn't result in a re-test of the 647
ductwork system. There were no 648
significant changes the air handling 649
#-VALIDGEN
units or internal components that 650 -#
would of meant new coil test sheets. 651 -#

Question 20 656

N.R - Did you think the contribution from the commissioning engineer helped in the commissioning effort, there experience of the systems?

G.W - I do actually, I'll tell you for why. The problem I find generally M&E services companies employ a site engineer and in fairness all of them employ a commissioning specialist because they don't have the in-house expertise of commissioning engineers and I don't personally think that they don't fully understand commissioning to its nth degree and on this job it was invaluable that we had a commissioning manager on the job because he just pulled all the elements of the commissioning together. Including all the test packs for the validation or to assist with the validation.

N.R - It was quite a complex system as well.

G.W - It was very much so with all the pressure regimes and the way the systems were integrated. I honestly don't think that a site engineer and a few commissioning guy's, run of the mill balancing technicians would have been able to do that job and having the expertise of a commissioning manager to pull it together, getting amongst it and understand how everything worked was invaluable.

Question 21

N.R - Do you think the validation work could have been carried out by the commissioning engineer?

G.W - No I don't think so. I just don't think that they would have had the expertise to do it.

N.R - Did the project actually finish on time or was it a bit over?

G.W - It was a bit over, I think it was a result of the routing problems and the co-ordination problem that had an impact and also there was some problems 'early doors' with trying to resolve the steel work structure, which was a delay in the procurement of the steelwork. I think ultimately it was possibly 10 - 12 weeks over. I think it was initially targeted around July time.

Case Study A

Interview with D M (C11 - Client Validation Manager) - 06/04/01

Key: C1 - Main Contractor 1, C11 - Client 1, Comm 1 - Commissioning Organization, VSP 1 - Validation Service Provider 1.

Question 1

N.R. - What were the main reasons for the building of the module (Pilot Plant)?

D.M. - Originally it was to find out if it would work or not. Weather the design of the whole project, because that was going to be the design for the rest of the project, so they were going to build a test prototype, which would contain both types of transfer systems. So they had equipment vendor x's system and the equipment vendor y's systems.

The initial idea was to build it and to see what problems there were or whether it would work alright and then to choose between one of them two systems.

See if they could get that bin to the top three floors up, see how feasible that was.

N.R. - and there was going to be a carbon copy throughout.

D.M. - That was the plan, only with one transfer system, not both of them, they were only going to go for one.

Question 2

N.R. - At what stage of the project was the validation activity start? Was it at the very beginning?

D.M. - In this case it was very early on because one of the very first design meetings, project team meetings, (C11 Managing Director), really not as early as it should have been, but early enough I think.

It involved the C1 people and it involved the design and GMP reviews

and stuff.

They were considering validation before the design was finalized.

N.R. - I believe the MCA came in at some stage and had a look at the design.

D.M. - I think they did.

$-TDEARL $-IMPLEMENTA
N.R. - Did they make a report ?

D.M. - I've seen nothing, with MCA they very rarely put anything in writing any way. So they probably just said if you were to build such a system it probably would be alright . That's the sort of comment the MCA make. They never say if you build that it will pass, they never say that. But they would say you've got no chance or don't build it like that. They never say it will be okay. Rumour has it that we were going to approach the FDA, although I don't think that they ever did.

N.R. - Would the FDA be looking at the same sorts of things ?

D.M. - Yeah, exactly the same things, only probably in a bit more detail. As
$-EXPSO
far as the module is concerned from the FDA's viewpoint, the GMP rooms
$-IMPLEMENTA
would probably be okay. I mean we couldn't really do much else (in validation). You could have video taped the air flows, there might be a few little things that the FDA would expect but they would be easy to do. If we just do what we thought we have to, to get it through the FDA. But the big problem with them is that room its in. I don't think they'll like that, warehouse. It was designed like that but I don't think they'll wear it.

Question 3

N.R. - Who was responsible for and who was involved in the validation activity?

D.M. - It was VSP 1, who we were then
$-VALIDFS
told we had to call C1. It was ultimately C1 and VSP 1 and then we had control over it, and then C1 did all the DQ's and started off doing all the documents for the IQ and OQ's and then we took over after we fell out with them.

N.R. - Do you know the main reasons why they discontinued there input in the project ?

D.M. - I think there was a lot of problems that were more or less contractual. We kept giving them changes in the design and they kept charging us money for changing it, which I think they were perfectly within there rights to do. Then there was conflict over how many changes they had done and what was a real change what wasn't, how much we owed them and there was a bit of personality involvement with MD and can't remember his name, they fell out and MD decided to get the price down. C1'S cost of validation was ridiculous it was very, very high compared with doing it ourselves and I think somebody went to C1 Plant x or y or somewhere some other plant. I think it was Plant x and found out this technique of using the operators to help with the OQ. So he said we'll do that here. That was virtually totally C1'S MD'S decision and that's what we did, as a cost cutting measure and to have more control I think and I think it was more efficient because if you get the operators involved your sort of training them as you go along. It was a good idea but they should have thought about that from the start.

#-COST #-TIMPLAN

Question 4

N.R. - I was going to ask who was involved at project inception, design, installation, commissioning but I know the answers to that.

#-VALIDDOCS

D.M. - well there was a project team, I can get you a copy of the original URS and from that URS a project team was set up. There is a validation committee as well, which only met twice!

Question 5

N.R. - The main scope of the validation activity was the validation of the equipment in the modules and the facility itself. What about process validation?

D.M. - That wasn't our.....the main thing was that there wasn't any change to process because they were already using 1000 kg for that product, product x. So the batch size hadn't been increased.

N.R. - So you have got a licence for that process, so you can take that and house it in another area.

D.M. - Yeah, Glen… there is a lot of PQ which was technical performance qualification but was in effect process qualification, although it was done with placebo no it was done with three live batches of product y. But it wasn't real product so it wasn't validating the process of making those tablets, it was just validating the procedures if it were from taking them from one bit to the other, which was the only bit of the process different it was just a transport thing. The actual making the tablets, the press was the same, the coater was the same, the blister packer was the same, it was only the transport mechanism between them that was different and with good justification I think that they didn't have to..they had to prove that they didn't smash the tablets up basically but it wasn't a change to how you actually make them. So they did the little PQ on the transport system but not the inherent process itself not the compression and coating.

Question 6

N.R. - How was the duration of the validation activity calculated? How did you work out how long it was going to take and cost ?

D.M. - We did it on our previous experience really, I mean the core of the validation activities as complete more or less on time. I mean the fact that it is not finished now is because we are waiting on the odd document. So the actual core validation was really almost on track, apart from some of the HVAC. It was estimated by previous experience because we have already done that type of kit and we know what the hourly rate is.

N.R. - Did any one use a matrix to calculate the times ?

D.M. - No it wasn't quite as elegant as that but there was a similar sort of thing. Cost we were only about 20% over. There was a lot of waiting for suppliers, a lot of commissioning engineers not turning up when they were supposed to and a lot of people

not being available at the right time. 257

Question 7 264
#-IMPLEMENTA
-#
N.R. - What level of compliance is to 266 |
be achieved ? 267 |
|
D.M. - Originally MCA, since it wasn't 269 |
designed to achieve FDA and it might 270 |
do in the future, we might have to do 271 |
some more work on it. I don't think 272 |
the MCA will have any problems with 273 |
it, its better than we did it before 274 |
but that's not a good thing to say. If 275 -#
an MCA inspector came along and said 276
how can you do this better than you 277
did before, but what you did before 278
was not very good. 279

Question 8 281

N.R. - Do you think the project was 283
sufficiently resourced ? 284
#-IMPCOM
-#
D.M. - It wasn't to bad it worked 286 |
quite well. Nobody screamed for more 287 -#
resource. We were given the operators 288
#-IMPRES
when we asked for them. We could have 289 -#
perhaps had a little bit more 290 -#
engineering support. On a busy plant 291
like this I think we did all right. 292
The project as a whole was under 293
resourced but that that prototype was 294
okay, it came in on time and started 295
up on time. 296

!-CONTRACT !-IMPCOM
N.R. - What about initial VSP 1 input, 298 !
do you think there was enough people 299
on that side involved ? 300

D.M. - We had a communication problem 302
rather than a lack of people. We had 303
the people there but C1 never because 304
there were so many different groups 305
#-IMPMEET #-IMPPER
working on it. There was us 306 -#
validation, there was C11 engineering, 307 |
there was the project team, there was 308 |
C1 and there was C1/VSP 1 and we 309 |
didn't speak to each other enough. We 310 |
didn't all get together often enough 311 -#
and talk about proper things. We got 312
together but those meetings were just 313
moaning on about cost and things. 314

Question 9 316

N.R. -Was there any group not 318

performing satisfactorily or any performing extremely well?
#-EXPIN

D.M.- VSP 1 were probably out of it by then, but they weren't very good to start with. They were very good in theory but they didn't do anything.
#-EXPIN

If we had of left it as it was, they would have written lovely protocols and stuff and when they had come up here they would not have had a clue. I don't know who were going to execute them. I mean we would have never got it done as quick as we had done because we knew what we were doing. That would have been a major..they would have been bad, they would have been sacked I would have thought.

Question 10

N.R. - Do you think that there was enough importance placed on the
#-TIMEIMPLEM
validation activity?

D.M. - Yeah, in this case there was. It could have been a little bit earlier but it was far better than anything that happened before and it was good enough I suppose.
#-IMPMEET

Question 11

N.R. - Do you think that there was sufficient site meetings and opportunities to review progress ?

D.M. - No. There was plenty of meetings but they didn't discuss the right thing.

N.R. - Was there a GMP audit carried out ?

D.M. - There was quite early on. There was several. The design itself was subject to a review , it seemed like it was three weeks but it was a full day GMP review. It went through raw materials coming in one end. This isn't just the prototype this is the whole thing , but the prototype was therefore part of the project. Raw materials coming in one end the finished product coming out the other and everything bit, did that comply with GMP? Did they comply with GMP? all the way through. List of bits that didn't, solutions, either engineer it out or change the process or whatever and once the prototype was built there

was a quality audit by the Q.P's (Qualified person). In fact there was two of them.

Question 12

N.R. Which people had the most input into the project?

D.M. - The project team really, but there was only two people that had the… the main players were Jim (engineering director), Glen (User group manager), you had a user and an engineer.

N.R. - What about from C1?

D.M. - The architect must have played a fair part, what was his name again?, once he had drawn it he disappeared off, and somebody else came in to build the bloody thing and you never dealt with anybody long enough to see who the key players where. There was the services bloke who did the.. in building the project there was probably a lot that went on that I didn't know about. C1 were obviously key players in that because they sub-contracted all the building works etc, I'm probably the wrong person to ask on that.

Question 13

N.R. - Can you describe an instance where the validation of the facility

#-TERINT

helped in overall project implementation ?

-#
-#

D.M. - There was the training of the operators, as previously described.

Question 14

N.R. - Can you describe an instance where validation hindered the overall project ?

D.M. - If you asked an engineer he might say…the good thing about it was we weren't driven by production. I f I said something like you can't do that, we need to do some more validation on it, the project team would listen to me because we weren't actually trying to be deadlined and run it to produce stuff before we validated it. Technically the functional testing was finished, of the equipment, before it was used. Because we were all in the team that was not a problem. How did validation hinder it. The key parts where the transport system stuff , you

#-TERINT

would have to ask equipment vendor A and equipment vendor B whether we messed them about by doing validation . Perhaps they explained things a bit more than they normally do and they were training as well.

Question 15

N.R. - Do you think that geographical location of the main parties had an effect on the project ?

#-IMPCOM
D.M. - I wasn't aware that C1 being located at York was a problem. VSP 1 being at Alton was a bit more of a problem. I find that some of these consultants are working on more than one project and get confused. I didn't really see a problem in terms of the validation but I only sat behind the desk and shuffled the reports from one end to the other.

Question 16

N.R. - During the project was there any significant changes to the facility or equipment ?

D.M. - The Accelacota was probably had to be put back together about three times.

N.R.- How did we address this from a validation point of view ?

D.M. - We had to virtually re-write a whole document and do the tests again because the first time we did the tests half of the things did not work. We had the manufacturer do a health check and fix it, so we had to print out some more tests, retest the ones we had already done. It was almost like a case of tearing up the first one and start again, but I didn't want to do that I wanted to keep a track of what was done.

N.R. - Did this extend the projects duration ?

D.M. - It just finished yesterday the Accelacota and they had to drill holes in the side to put extra dials on , they had to put the controls for the feed station. They had to put two extra water pipes on the back, the clean in place would not work. It was not handled through change control because it was never set up and working, it was an on going thing doing the validation so it wasn't constant deviation from the validation and failed tests that had to be

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  rectified and tested again. There was   513
  a lot of problems with the kit.         514
  Another example was the compression     515
  room were the hoppers did not fit that  516
  was just a badly designed room which    517
  was technically our fault because       518
  somebody got the dimensions of the      519
  hopper wrong or the dimensions of the   520
  press wrong. So those hoppers had to    521
  be changed and run without the          522
  automatic hopper collection system and  523
  timer and had to be filled by hand for  524
  the first couple of months till we      525
  got, cause the de-dusters did not fit   526
  between the compression and the hopper  527
  , so they had to buy new de-dusters.    528
  So that was a problem right from the    529
  start, from design and when you         530
#-EXPIN
  actually got the kit in there it        531  -#
  didn't bloody well fit.                 532   |
                                                |
  N.R.    - Did the validation provider   534   |
  seem to fully understand the clients    535   |
  requirements ?                          536   |
                                                -#
  D.M. - No. But then again we kept       538
  changing what the bloody requirements   539
  were.                                   540
#-EXPIN
                                                -#
  Question 17                             542   |
                                                |
  N.R. - Did the client know what was     544  -#
  required for GMP ?                      545

  D.M. - No. In terms of GMP they knew    547
  what they wanted. But there are         548
  several ways of complying with GMP. We  549
  knew what the GMP requirements were     550
  but we didn't know what the design was  551
  we wanted. For the prototype once we    552
  got the design going that was it but    553
  for the whole project we kept changing  554
  it and changing it.                     555

  Question 18                             557

  N.R. - were commissioning contractors   559
#-VALIDDQI
  used to assist in validation of the     560  -#
  facility and equipment ?                561  -#

  D.M. - For the DQ they were and then    563
  they were left on there own. You have   564
  to remember that all equipment apart    565
  from the transfer system, all you had   566
  to do was move it from one end of the   567
  plant to the other. It wasn't like we   568
  were buying new stuff. If we had        569
  bought a new blister packer and         570
  compression machine I would have        571
  thought that the vendors would have     572
  been a lot more heavily involved in     573
  the validation.                         574

  Question 19                             576
```

N.R. -Do you think that the vendors in most instances could actually carry out the validation ?

D.M. - Yes. We would always take there validation documents and have a look and it depends on the price if we use it or not and how good it was. But anything for an easy life , we get them in, there documentation, put our front cover on, let them do the work and we will witness it and if there is any additional tests they or us can do them. The problem with doing that is that they will design the qualification so that there equipments passes. So you have to make sure and stress that that they are doing the right tests.

FREQUENCY PRINTOUT 07/07/2005 09:54:45 Page 2
(Top PCT is % across files. Bottom PCT is % within the file.)

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		0.00			0.00			0.00
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Manually Coded Data – Case Study A

Qualitative Data – Code Sheet

A1.

Date : 31 August 2000 **Ref** : 1484j88_d

Subject : **IQ/OQ Documents for Prototype**

[redacted] have reviewed more of the IQ/OQ documents from [redacted] which ar still not satisfactory. Comments are given below but I have not forwarded them to Graham [redacted] Since Graham has not replied to any of my previous three memos, perhaps we should leave these comments until we can arrange a meeting. I would be grateful for your comments.

73 18 18

Dave

[redacted] Validation/BAPK Manager

A2.

Equipment Numbering / Tagging problems	Action
[redacted] to supply database of all equipment tags.	GW
Meeting to be held within [redacted] to discuss "ownership" of the database and combining with existing.	DTR/PC
Updated drawing required showing all tags.	GW
Dust grilles to be tagged.	GW
A number of tags are still required, [redacted] are addressing this.	GW

87

A3

Other issues

[redacted] did not witness the HEPA filter smoke tests. Data and documentation from the tests to be supplied to [redacted].	GW
Decision on repeat tests to be taken once test data has been evaluated	JM/DM/ [redacted]

76 22 29

Qualitative Data – Code Sheet

A4.

63

Calibration to be performed to current ISPE standards, SOP to be written retrospectively.	Quality PD/DcG

A5.

87

83

		Action
1	**Objectives:**	
	The objective of the meeting was to identify any outstanding issues with regard to the calibration and validation of the building services within the prototype modules.	
2	**Critical Equipment Assessment Ref. memo 1484jo3** [redacted]	
	Instruments to be calibrated during w/c 16th Oct. Possible problem with the location of combined temperature and humidity detector in the packaging area.	PD/DcG

A6.

18

27

Area	Specified Design Differential (Pa)	Actual Differential (Pa)	Compliant (yes/no)	Note
Packing				
PAL to Host	30	32	Yes	
MAL to Host	30	35	Yes	
PAL to Packing	15	16	Yes	
MAL to Packing	15	15	Yes	
Cooling				
Cooling to host	30	7 to 45	no	DP fault light was on during the test.
Mal to Host	30	23 to 38	no	The system appears to be 'hunting' due to inter
PAL to Host	45	43 to 65	no	of the several control loops which control fresh
Solution prep to host	15	5 to 23	no	volume, and supply and extract frequency inve
Compression				
Process Lab to Host	30	35 to 38	no	The process lab to host door requires attentior
Compression to host	15	9 to 13	no	

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Qualitative Data – Code Sheet

18

A7.

All

The schedule provided by [redacted] is not correct and cannot be used

We need a meeting to discuss what [redacted] have provided and how we are going to manage the system in the future

Can you attend a meeting 10.00am on Wednesday 8th in Engineering to discuss this

David

_____ Reply Separator _____

Subject: Calibration Certificates
Author: [redacted] at GB[redacted]-Pharma
Date: 06/11/2000 10:29

Dave

We're busy completing the calibration documentation but one issue which is still undecided as far as I'm aware and which could hold us up is the plant numbering system.

Have we had a revised list from [redacted] containing references for all the new kit?

We were also planning to align the instrument tagnames with the plant numbering system which would, for instance, mean changing the tagnames of the instruments on the Accelecota. Currently we're unsure what 'rules' to follow when assigning these new plant numbers/tagnames.

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A8.

d). Validation documentation

A brief meeting was held on site between [redacted] to review the documentation required by yourselves to complete the validation exercise and [redacted]s have gone away to pull together the relevant commissioning documentation which will be supplemented with manufacturers literature and certificates of conformity for plant & equipment from the final O&M manual.

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Qualitative Data – Code Sheet

A9.

Meeting to be held, Friday 13th October, 11 am – Engineering

1. Objectives of the meeting.
2. Critical equipment assessment (ref memo 1484jo3_[redacted]) – calibration r
3. Non-critical equipment – who calibrates, when, how. L&G? [redacted]?
4. Equipment numbering, and general problems– ref memo 1484jo1_[redacted]
5. Tagging problems– ref memo 1484jo2[redacted]
6. Dirty filter tests – re memo from [redacted]
7. Other issues

30

88

A10.

1). Issue of Operating & Maintenance manuals and as-fitted drawings.

The draft mechanical manual is now back with [redacted]s for updating following comments from both ourselves & [redacted]r and we would hope to have this available for issue within the next 7-10 days.
The electrical manual (draft) is expected from [redacted]s this week and we will arrange for this to be delivered to site so that your staff can comment on this as required.
As-fitted drawings are currently being finalised by our cad team and these should be issued within the next 10-14 days.

30

2). Labelling of equipment.

Unfortunately a number of labels were manufactured with incorrect references and these are now being re-made. We would hope that these will be delivered to site and fitted before next week.

Qualitative Data – Code Sheet

A11.

Dave

Previous experience suggests L+G calibrations are inadequate. If they are calibrating items then I suggest we see the procedures that they are intending to use and/or witness the calibrations.

Dave

87

52

_____ Reply Separator _____

ubject: Module calibration
uthor: David [redacted] at GB-[redacted]
ate: 10/10/2000 16:29

Further to this mornings meeting with [redacted] to review progress we discussed calibration of instrumentation. It occurred to me that we should not be calibrating building services equipment. I have checked the situation with [redacted] and they have confirmed that Landis Gyr are calibrating such things as sensors and [redacted] who are commissioning the air conditioning equipment are using traceable instrumentation and that this information will be handed over as part of the commissioning documentation. The method of calibration may however not be acceptable and not all of the equipment may be critical.

We need to discuss this with [redacted] and agree the methods they are employing is acceptable

I know this is an Engineering and QA issue but could I ask Dave [redacted] to coordinate our requirements

A12.

Assessing the time required for execution is difficult since the fine detail of the modifications to existing equipment and the design of new equipment is not yet available and the complexity of the OQ testing is not yet known. In addition, the experience of the 'executor' has a large bearing on the time taken and some of the new equipment and/or modifications may mean that the equipment is not familiar to the operators.

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Qualitative Data – Code Sheet

A13.

Commissioning/ O&M Manual.

Information Required

Filtration

1. HEPA filter test certificate for the second HEPA (FTH/09/138/02) is stated as having a location in the compression suite – a new cert. is therefore required. The test result sheet and layout drawing will also require alteration by Puraflow.
2. HEPA filter certificates of conformity: - the first certificate in section 9.1 refers to 5 no Airopac 3GGMHF 12245-90 filters. What are the tag numbers of these filters? Where are they installed? The delivery address on the cert. is Barnet and Graham , Manchester?
3. HEPA certificates of conformity:- this certificate is for 10 No. MGA-2GW-01PU filters which are EU14 graded, the [redacted] drawing 396256/M/9004/SE/G states the filters are to be EU12. Which filters does this relate to? Tag No. and area? We have 6 No. terminal HEPA's in this installation and it is unclear which certificate relates to each filter.
4. Section 9.2 only relates to 3 filters, we have more than this installed!
5. There are no certificates for any panel filters.
6. Section 8.17 – BAX filters?
7. Section 8.16 refers to panel filters. The information in this section is for bag filters.

Instrumentation

1. All controls/ instrumentation details are required (Siemens equipment etc).

Building Fabric

1. All room fabric details are required.

Qualitative Data – Code Sheet

A14.

I have completed the validation costs spreadsheet as requested and details are provided below.

It should be stressed that these figures only take Validation Section personnel into account. Costs for Metrology, Engineering, Training and Production Departments who will be involved are not included. Furthermore, I am not sure what [redacted] intended regarding Performance Qualification as I was under the impression this was a [redacted] responsibility. PQ tests have not been included.

45

Also, the costs for the main project are based on the facility validation plan prepared by [redacted] which requires review and may not accurately reflect the current design. These costs an only be described as rough estimates.

For IT systems, we do not have the expertise in-house for the validation of complex computerised systems (especially in terms of 21 CFR Part 11) and have relied on contractors/consultants (Tony [redacted] etc) in the past. The in-house costs for this are therefore the same as quoted by [redacted].

6

A15.

Our validation staff can execute an OQ protocol within 0.5 to 2.5 days depending on the complexity of the system. Each system in the prototype module has been assessed and time to complete the validation has been estimated. These times (estimated by [redacted] Process) are shown in the attached table. Although experienced validators could take less time than indicated, I am in agreement with the times provided due to the unfamiliarity of some of the systems. The total man days required for IQ and OQ for the prototype module is 98 days.

2

A16.

[redacted] to forward amended Functional Specification by week ending 13/10/00.

70

All HEPA filters have apparently been tested but the tests were not witnessed by [redacted] personnel (neither validation nor engineering) and there is no documentation. These tests will need to be repeated.

30

Qualitative Data – Code Sheet

A17.

Compression Module

1. Air handling unit Magnehelic gauges have not been tagged.
2. The heating coil has no tag.
3. All filter pressure switches still have filter tags.
4. Variable speed drives and have no tags.

Coating Module

1. All filter pressure switches still have filter tags.
2. Attenuators have no tags.
3. Variable speed drives have no tags.
5. Air handling unit Magnehelic gauges have not been tagged.
4. Panel filter has incorrect tag.
5. Automatic damper on extract has no tag.
6. No room tags for filters, grilles etc.

87

Packing Module

1. Panel filter tag incorrect.
2. Air handling unit Magnehelic gauges have not been tagged.
3. All filter pressure switches still have filter tags.

A18.

David,

further to our recent meeting to discuss outstanding issues on the pilot plant we would advise you of the folowing:-

We will be on site on Friday 15th Dec. (PM) to clean out the roof void above the LTHW plantroom. In addition to this we are meeting a representative from Spirax Sarco to hopefully establish what the problem is with the Ogden condensate pumping set.
With regard to the O&M & validation documentation we would hope to have the filter certificates of conformity in our possession by Friday and if so will give [redacted] an advanced copy.
We have requested [redacted] issue the final O&M's to us by no later than 15/12/00, and if they comply with this request we will forward these onto Martin [redacted] for onward transmittal to yourselves.

87

88

Qualitative Data – Code Sheet

A19.

Project [redacted] Prototype Instrumentation.

The following points have been raised and require some discussion;

1. Is the SOP for instrument assessment to be used?
2. Are SOP's required for each calibration procedure?
3. Should the plant numbering system be used as the sole method of dentifying instruments? ie. replace exdsting instrument identification system.
4. Should calibration be carried out at loop or component level?
5. The URS should be reviewed to verify the required accuracy.

86

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Qualitative Data – Code Sheet

A20.

IQP-1003-A

Page Ref.	Comment IQP-1003-A
Front Page	IQP-1003-A Is this the correct format? No equipment identification numbers.
9	Bullet points?
9&10	The test description does not actually describe the method of establishing the material details of the enclosure building fabric. 'Walls' does not constitute a test description. The enclosure material details should be collected from the enclosure manufacture. These certificates of material conformity should be used as the basis of confirming construction details. No tag numbering system used to identify specific pieces of equipment.
17	Document default template details left in document.
20	No details of Magnahelic gauges. Magnahelic is a trade name of Dwyer instruments Inc and the model number will be a function of the differential pressures set out in the OQ, so at this stage this data should be available for use in the IQ?
23	No method given for taking utility readings.
26	No details of the approved preventative maintenance program mentioned in the acceptance criteria section.
28	Materials of construction section is missing?

IQP-2003-A

Page Ref.	Comment IQP-2003-A
Front Page	IQP-2003-A Is this the correct format? No equipment identification numbers.
3	Shouldn't the third para in the description also mention that fresh air is also used for occupant ventilation requirements. The unit is also fitted with Magnahelic gauges which are not mentioned.
9	Data such as filter details, supply fan, heating and cooling coils etc are known. Why are these not input into the table? One AHU serves this area according to your description , no other coils are mentioned until the equipment installation section.
12	Electrical panel checks are not required as part of an IQ. The panel has no identification tag. Such detail as wires with pin crimps is not required for GMP testing documentation. How do you determine if the cable trunking is of a satisfactory size, no test description is offered! To satisfactorily determine if the trunking is correct it would require a calculation of cable sizes, applying grouping factors etc. as per the current IEE regs. The test ' the panel is clean and tidy' has no immediate effect on product quality and therefore not needed. There is no mention of 3 port valves and actuators and the actual variable speed drive mentioned in the description (of which details exist!). Is ductwork really needed? You don't attempt to identify it with

33

73

Qualitative Data – Code Sheet

A21.

76

IBC Unloading Station to Packaging

OQP 6001-A

Page 4	Objective – text incorrect.
Page 4	Description and scope – manufacturer?
Page 6	Procedure – no need for bullet point. No[redacted] format
Page 7	Results –[redacted]should be able to provide model and serial numbers for inclusion in expected results.
Page 12	Panel checks – commissioning.
Page 13	More information should be available.
Page 16	Documentation – comment as other IQ's – material certificates, calibration certificates etc in wrong section. Who is writing the referenced SOPs – are these from Gallay? Utility consumption??, Spares?
Page 19 - 21	Drawings – not as[redacted] instruction.
Page 23/4	Instrumentation – No information?
Page 27	Utilities – where is the vacuum reference from? FS only indicates electrical and compressed air.
Page 29-30	Maintenance – no[redacted] format
Page 32- 33	Materials of construction – section not as template.

HVAC Documents – Comments from[redacted]

HVAC and environment documents do not recognise the difference between commissioning and validation.

OQP-2007-1

Page Ref.	Comment OQP-2007-1
4	PRO 002, MAL PRO 003, PAL PRO 004 or PRO.002., PRO.004, PRO.003
4	Capital E for enclosure.
4	Filters - H12 (EU 12 on AHU manufacturers records?)
4	"No specific air cleanliness class is designated for any of the rooms". If no class of cleanliness is specified why provide a 'GMP' enclosure and grade 12 HEPA filtration? At present the tablet packaging function is carried out at grade 4 and 7 filtration.
4	Description does not state the fresh air load for occupant requirements. What is the fresh air quantity based on?
5	Why mention safety guarding and emergency stops in the principle section. They are not normally features of facility rooms of HVAC

Qualitative Data – Code Sheet

A22.

Page Ref.	Comment OQP-2007-1
	plant/system. Just write 'not relevant to this protocol' as per system backup and recovery.
5	Security features such as password protection for variable speed drives should be considered.
13 test 1&2	Description sections are used to provide a procedure to follow to execute a test and not just a statement. The description in the first section of this test is in-fact the expected result. Where are the status lights positioned? Pre-set delay – how long?
14 test 3	No mention of method of simulating a power failure.
18	Procedure and apparatus – Is velocity or velocity pressure being measured directly from the micromanometer? If VP amend procedure? Confirm status of room – is it 'at rest'. Equipment volume has to be considered in the calculation as this may well greatly reduce the change rate to less than the GMP minimum.
19	No expected result? What happens if for large ducts more than six positions are needed. What calculation is used for converting Pascals to velocity.
20	Where does + 10% come from CIBSE, BSRIA, ASHRAE?
29	What method of 'securing dampers' will be employed? A one off measurement of differential pressure is not satisfactory for GMP purposes. A real time record related to room operating patterns should be provided as evidence of compliance. It is normal GMP to provide an alarm for room differential pressure to indicate to the operator that the air change rate has reduced to an unsafe level.
34	What is the procedure if a filter fails? What about duct leakage testing after the HEPA's?
42	'Take a lighting measurement at a height of 1000mm above the floor'. Should the lighting level be that of the actual operator working plane? Which lighting code does this procedure come from, is it CIBSE?
47	Where does ' HVAC system must have been operating continuously for at least 24 hours prior to the commencement of the test' come from? Why must we make sure that the process equipment within the room is not in operation? The whole purpose of this test is to test the operation of the HVAC plant CHW, LPHW coils and air diffusion success against the pre decided GMP values of temperature and Humidity. Is the design temperature based on dry resultant temperature or air temperature? Sampling intervals of 5 minutes seem too large where does this come from? How long are the loggers to be employed in the rooms (should be related to room occupancy/shift patterns)? Consideration should be given to the temperature mapping arrangement? There is no mention of a low limit for humidity? Again, it is normal GMP to have facility alarms for temperature and humidity non-

33

18

Qualitative Data – Code Sheet

A23.

18

Page Ref.	Comment OQP-2007-1
	conformance. Note- If any hygroscopic tablet packing is to be carried out in the area humidity levels in excess of 30/35 % will effect product!
52	The description column should be used for conveying the specific test procedure to achieve an expected result and not just a statement related to the test! The procedure section is too vague. Provide details of times and dates etc.
54	No indication of which test specification is been adopted? BS? Federal Standard? It is stated at the beginning of the protocol –NO SPECIFIC AIR CLEANLINESS CLASS IS DESIGNATED FOR ANY OF THE ROOMS. –What is the point of carrying out a test for 'at rest' and 'in production' states if there is no pass or fail criteria? We are therefore not testing the HVAC plant or room design, just recording whatever conditions occur on the day! The essence of a GMP enclosure design is to adopt the current GMP performance levels prevalent within the industry to provide a suitable environment for the activities to be carried out within the facility.
58	Comments as above. This is not a test!
62	As above.
66	This section does not cover GMP alarms! Which alarm is actually triggered if the supply AHU fan fails? Where are the Filter alarms – in room ? plantroom?. For GMP purposes it is generally accepted that if regular monitoring of filter pressure drop is adopted no alarms are necessary. The fundamental principle of GMP alarms has appeared to have been overlooked.

Qualitative Data – Code Sheet

A24.

Page Ref.	Comment IQP-2003-A
	a tag? What is important is that we are presented with the correct air volumes (tested in the OQ).
16	Document location should be entered i.e O&M Manual? Commissioning engineers report? Air handling air leakage tests will be required these where carried out by the manufacturer. Shouldn't the efficiency of the HEPA test certificates exceed 99.5%
23	Pressure difference filter (FPN/09/135/02) is not an appropriate reference for a Magnahelic differential pressure gauge, it refers to a filter. Again the details are known and should be entered. No differential pressure gauge is fitted across the fan. Supply air pressure probe and temperature probes – details should be entered prior to test execution.
28	No values given for CHW and LPHW ? Where are the tags in question to be fitted? Are they at service entry into the AHU? At source? No method of measurement offered.
31	Details required.

18

Qualitative Data – Code Sheet

A25.

Progress Meeting

Date: 10/10/00

Present:

Summary

1. Packing area Magnehelic gauges have been calibrated. One, possibly two, will need to be replaced. D.M. awaiting information from Dwyer Instruments Inc. with respect to acceptable tolerances for the units.

2. A LEV extract is required for the solution preparation area – G.W. to investigate effects room pressurization.

3. [redacted] to forward amended Functional Specification by week ending 13/10/00. 70

4. All Prototype Module HEPA filters have been tested without being witnessed by Engineering or Validation representatives. 49

5. [redacted] and Siemens suggest that the controls functional demonstration for each of the three areas be carried out over a 2 day period, instead of at different times. 02

6. A revised drawing – HVAC SCHEMATICS No. 396256/M/9004/SE/G was passed to [redacted] for comment. (Comments to follow).

7. Tag database will be forwarded to [redacted] by Alan [redacted] for comment

8. D.M. reported on instrument calibration issues such as SOP's for calibration procedures, instrument assessment and the current component numbering system There was a general agreement that the area required further detailed discussion.

9. D.M. highlighted that the installation of a number of control detectors required attention as the present installation method prevents the detectors being removed from the ductwork to allow for calibration.

10. It was a agreed that validation and engineering would identify critical systems that require immediate calibration. 52

Manually Coded Data – Case Study B

Qualitative Data – Code Sheet

B1.

The Design Approval Forms are now logged in the Validation Status Report - xxx, 9/4/02

Design Approval Forms Log

Ref	Date Raised	Equipment	Reference to spec/URS/RFT	Location
1	11/12/2001	Air supply to MALS and PALS serving low RH areas	Project XXX overall URS, URS-09-1	Filed with URS-09-1
2	28/01/2002	Room pressure monitoring/alarm in Zone 3 areas	Project XXX overall URS, URS-09-1	Filed with URS-09-1

45

Qualitative Data – Code Sheet

B2.

GMP Upgrade Project

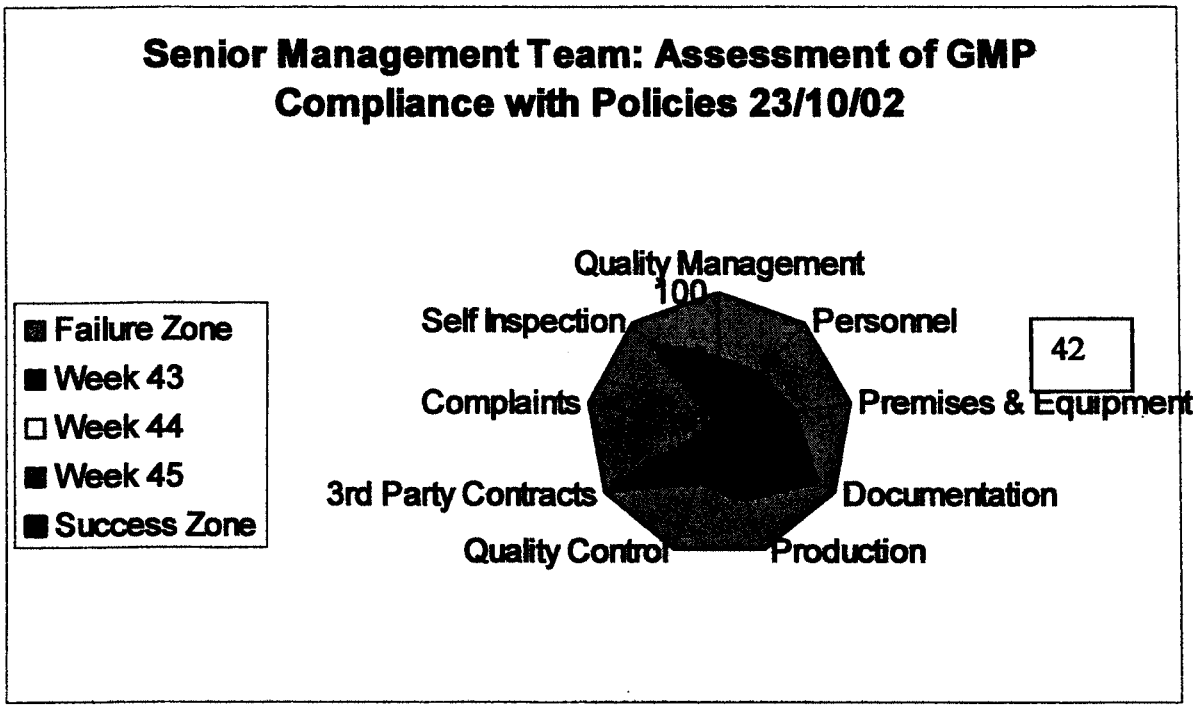
GMP Assessment Form

Department/Area:
Author:
Date:

Key Requirements		System	Implementation
1.7	Regulatory Compliance		
1.7.1	Comprehensive procedures need to control incoming approved regulatory changes and outgoing proposed regulatory changes.	0	1
1.7.2	All site activities will be in accord with the need for regulatory compliance.	0	1
1.7.3	Operational units will arrange activities such that they are in line with the regulatory requirements.	0	1
1.7.4	Regulatory department will minimize the negative impact of regulatory change on operational activity.	0	1
1.9	Validation		
1.9.1	Validation is performed on facilities and equipment, cleaning procedures, analytical procedures, production processes and computerized systems which have an impact on product quality.	0 41	0
1.9.2	Each aspect will be covered by validation plans and protocols which will contain a specific and detailed description of the validation activities and the acceptance criteria.	1 42	1
1.9.3	A consistent approach to validation provides documented evidence that systems are suitable for, and consistently perform, their intended purpose.	1 42	1
3	Premises and Equipment 40		
3.1	Environment Control		
3.1.1	The environment is controlled to avoid difficulties associated with weather or pest ingress, extremes of temperature or humidity and contamination by micro-organisms.	0	0
3.1.2	The control of pests such as rodents, insects or weeds frequently uses chemical substances, which must also be controlled.	1	1
3.1.3	Only approved herbicides, rodenticides and insecticides may be used, the time and point of use and storage of such materials is subject to prior approval. Wherever possible mechanical devices such as insecticutors or humane traps are preferred.	1	1
3.1.4	The Company takes care to ensure that none of its activities impact negatively on the immediate surrounding residential area, and controls all noxious emissions within statutory limits.	1	0
3.1.5	The routine management of environmental control activity is the shared responsibility of the Engineering Department and the Safety and Environment Department.	1	1

Qualitative Data – Code Sheet

B3.



B4.

Diary Memo.

MCA Site Visit

Resources

1 Auditor 16 to 18 July 2002

Reason for Visit 18

Observations 27

'Verification of containment by use of alarms or continuous monitoring'. 30

Qualitative Data – Code Sheet

B5.

Validation Manager 10/09/2002

Memo Notes

Minutes of meeting - Me 84

CLARITY OF SCOPE
All utilities and room finished (includes solvents, gases etc) 22
DQ? **Me.**

Floor plan – Services Engineer? and Line diagrams (P&ID) – Services Engineer? Esp Central Core (protocols ready 2 weeks before commissioning). **John to see Owen about these.**

No tolerences on pressures etc. **Me – bob, Owen, Greg** 22

Meeting just after shutdown but need to meet before then to transfer P&Ids etc. 27

Line diagrams/flow charts of process – boxes to include ID of equipment, Validation database no, status of validation. Tie in with Chris's flow charts of processes (eg the one in). **Me**

Lubricant grades – I'm supposed to be getting this? – FDA document – **John to search.** 19

Document for review from Stuart. **Me/John/QP (Greg)** 23

Calibration an issue, resource tagging? Resource for Metrology? **Me?** 23

Commissioning/ validation Planning and Gantt charts. Defining scope of systems. – **Me/John**

Asset numbering? Quantity Surveyor **??????????**

Qualitative Data – Code Sheet

B6.

Phases - Key Dates

Phase I

⇧	1/3 Warehouse	Nov 2001 - Sept 2002
⇧	Central Core	Oct 2001 - Sept 2002
⇧	4 Compression Cubicles	June 2002 - Nov 2002
⇧	Coating	June 2002 - May 2003
⇧	[redacted] Granulation	May 2002- Feb 2003
⇧	Granulation Multi Products (5/6)	Sept - Oct 2002

Phase 2

⇧	1/3 Warehouse	Oct 2002 - March 2003
⇧	1/3 Packaging	Oct 2003 - May 2003
⇧	3 Compression Cubicles	Nov 2002 - Feb 2003
⇧	Effervescents Manufacturing	June 2002 - Jan 2003

[redacted]

29 | 83

29 | 05

Phases - Key Dates

Phase iii

⇧	1/3 Warehouse	April 2003 - Oct 2003
⇧	3 Compression Cubicles	Mar 2003 - June 2003
⇧	2/3 Packaging (inc. Efferv PK)	July 2003 - Dec 2003

Phase IV

⇧	Warehouse Despatch Goods In	Oct 2003 - April 2004
⇧	1/2 Demolition of external areas	

Phase V

⇧	Sprinkler Tank Homogenisation Tank	Feb 2004 - July 2004
⇧	1/2 demolition of External Area	
⇧	End of Cladding	
⇧	Celebration Party	

[redacted]

Qualitative Data – Code Sheet

B7.

PROJECT xxx
MEETING HELD 10th JANUARY 2002)
(REF : PROJ2003/MINUTES/REV100102)

1. OVERALL SITUATION

Central Core and Warehouse Phase 1 isolated and handed over to C2. Asbestos removed in Central Core.

52

11/10/01 DM will produce proposals for approval of drawings/specifications/URS by October 17th.

Next major issues

Communication improvements.
PL 15/02/02

28

PROJECT xxxx
MEETING HELD 21st FEBRUARY 2002)
(REF : PROJ2003/MINUTES/REV210202)

1. OVERALL SITUATION

24/01/02 Central Core, warehouse and tower are being demolished.
21/02/02 Very little attendance at this meeting for the 2nd consecutive time.
22/02/02 Very little attendance at this meeting for the 3rd consecutive time.

28

PROJECT XXXX
MEETING HELD 5th SEPTEMBER 2002)
(REF : PROJ2003/MINUTES/REV050902

1. OVERALL SITUATION

05/09/02 Central Core – Partitioning walls around booths being installed

Central Core

05/09/02 Official opening now planned 11/11/02

49

Qualitative Data – Code Sheet

B8.

PROJECT 2003
MEETING HELD 21st MARCH 2002)
(REF : PROJ2003/MINUTES/REV210302)

21/03/02 Mail received from Architect mentioning late drawings because of absence
of manufacturer's information (Glatt).
Dust extraction, Air handlers larger than on first drawings prepared by Glatt.
Until order is placed with Glatt, we won't be able to get into details –
- Negotiations to take place in April.

22

Central Core

21/03/02 Cl1 still must provide the following information :
- Liquid dispensary : details of display panel (weigh scale)
- Floor topping (choice)
- Ceiling (choice)
- Bin Wash area : location of console
- Light beams on conveyor : energy and location
- Access gantry details (provided by Gallay, bin washer)
- Clean part wash area : choice
- IT requirements in admin part.

22

Qualitative Data – Code Sheet

B9.

Validation Manager – Memo/Notes

Things to do for VSP 2.

Collect for validation engineer – room specs/

Call Services engineer – Where's my stuff and Need identification for things such as Air Intake Grilles – are these marked in the Design drawings? 87

Owen –the chart recorder appears to be located in a plant room. What procedures will there be to note the room conditions prior to working? Would it not be better if this was in the dispensary office where it could be monitored constantly? Also, where are the magnehelic gauges to be located? It should be noted that we should start monitoring these conditions from the date of handover. 45

Chris XXX/Owen/Pascal etc: Could you give Stuart XXX of VSP 2 a ring (or Email to XXXXX.fsnet.co.uk regarding compressed air purity. 32 45

Note that some companies have been requested to increase their monitoring of purified water and compressed air systems for 90 days following a break-in to the system. 49

Calibrations?

How do we intend to get all the services equipment registered on maintenance system? It's possible to get the GMP critical equipment from the IQ protocol, but for non-critical equipment, who's going to go through the drawings and register everything? Bearing in mind it has to be completed by 5/11/02 28

This leads on to an even bigger "opportunity". Maintenance schedules for GMP critical components (of the HVAC) system for example) must be prepared and approved before the validation reports can be approved. These reports must be approved before routine production can begin and inspection.

Not only do approved schedules need to exist, if they are different from the manufacturers recommended procedures, the differences must be justified and documented. 30

Spares lists are also required and again, if the spares we decide to keep in stock are different from the manufacturers recommended list, the differences must be justified and documented.

This is a major amount of work which may need extra resource to complete it on time. This resource is available (from VSP 2 for example, but it would cost). 28

QA – Documentation archives. The Project is going to create a huge amount of documentation and the roll racking in QA is almost full. All GMP critical documents which form part of the validation need to be stored in a controlled archived. (Engineering and operators will have copies of relevant documents). Porta-cabin for temporary storage? Can we use Microbiology in the short term. 21

Owen - drawings, Controlled drawing should have a C11 box added for approval and they should be in a controlled storage area. Note also that if drawings included in validation protocols are red-lined, the final, properly approved drawings should eventually exist and must match those us[illegible]dation. 21

Dave XXX/Pascal/Owen/Chris/Chris etc/ Work instructions. For the dispensary and central core

Qualitative Data – Code Sheet

B10.

Project XXXX

Invitation to Tender for Detailed Design

January 2001

Overview

Project XXXX covers the major fabric and infrastructure upgrade of the XXXX site and has reached the detailed design stage. A global design concept has been agreed and it is proposed to progress this to the detailed stage enabling tenders to be obtained for the construction. This document sets out the outline project specification, the scope of work envisaged for the detailed design stage and the timescale required

Scope of Work

'Provision of support documentation for Validation requirements'. 86

Qualitative Data – Code Sheet

B11.

12/02/03

PROJECT [redacted] GENERAL MANAGEMENT

⇒ The Project is very late:
* [redacted] June instead of February
* [redacted] Compactor June instead of February
* [redacted] Coater September ? instead of June
* Total completion now in 2005 instead of July 2004

C2

⇒ No synthetic view of the Programmes:
* The programmes are driven by [redacted] we have no way of checking that they are not late.
No counter-power to [redacted]
No monitoring.

24

⇒ No view of general progress of the Project:
* We cannot answer straightforward to the progress and situation of each area.
* No proper reporting

24 28

⇒ Costs are not under control any more:
* No detailed forecast
* Costs forecast well over budget (£ millions)

⇒ Resources insufficient:
* One cause of the delays and the lack of control on programmes and costs.
* Resources not dedicated therefore not focused on key sub-parts of Project.

2

⇒ Result:
* Poor communication (costs, programmes, technical situation)
* No transparency
* It is not possible to get any confidence in what is assumed.

31

⇒ **Remedies:**

- **Additional resources - Technical, Planning, Project Management**
- **Reorganisation to focus individuals on activities and areas**
- **Report scheme redefined (+ proper meetings)**
- **External help on specific topics (Costs, funding, etc....)**

Qualitative Data – Code Sheet

B12.

Date : 28 October 2002 **Ref** :

Subject : **Dispensary Building Works**

Dave,

[redacted] and I have conducted a brief survey of the dispensary area this morning – we hope that this information is of use for any of the progress meetings that you are attending this week.

For a more detailed break down of our findings, see table overleaf. A general list of comments is described below.

General Comments

- Doors are missing from some of the rooms
- Sprinkler heads to fix in all areas
- Wall and floor finishes to complete and seal
- No Magnehelic gauges external to dispensaries are installed
- No windows installed in any areas
- Some of the installed doors scraped (damaged?)
- Wall panels appear to need re-fixing (popped out strips)
- Draw Pull Cords shedding fibres, excessive lengths.
- Any Sealing etc between wall panels/skirting is yet to be completed
- Area will require considerable cleaning

Installation Qualification

In addition to this survey of building works we have also noted information required for IQ of the dispensing booths supplied by Extract Technology. Upon consultation with the approved documents we have noted a number of discrepancies between the documents and the plant installed (installed components differ to those expected in the protocols).

In addition, the Drum tipper tag reference in dispensary 1 refers to dispensary 2 system (and vice versa). Drum tipper in dispensary 3 is not tagged.

Regards

73

Qualitative Data – Code Sheet

B13.

MON 16/12/02

Updates:

IQP 1214 ENV. MON

63 52

- Installation: Tags required
- Documentation: To sign (GS)
- Drawings: To review (DJM)
- Instrumentation: Id tags, Cal stickers to check, TX's to calibrate when replaced
- Utilities: To review (DJM)
- Maintenance: section to write up – probably none – done via calibration/replacement (GS)
- Test Instrumentation: Cal cert for Fluke multimeter (GS)
- Attachments: Sheet to write up (GS)

IQP 1178 & 1179 HVAC

- Installation: Tags, lagged items, no access – poss use comment of "red lined drawings" and system performance? (JM/NR/SW)
- Documentation: [redacted] available "mid" week [redacted] – Monday PM, Barkell – [redacted] chaing up on Monday (JM/NR/SW)
- Drawings: Red line exercise done on Saturday – drawings to be amended by Ductform (via instruction from [redacted]) Expect news on Monday. Revised drawings will be signed as "as installed" 87
- Instrumentation: CR04/01 cert available, need to check tag and cal sticker in place (also for humidity probes and indicators). TX comment as env. monitoring
- Utilities: Steam has been off all weekend, therefore LTHW temperature not correct – hopefully be back on Monday AM. (If it is not, temperature study will be affected – loggers are programmed to start at 09:00, 16/12/02)
- Maintenance: To verify (NR) 29
- Materials of construction: To verify (NR)
- Test Instrumentation: To complete when document complete (JM)
- Attachments: To complete when rest of document complete – probably will only need signing off

IQP-1221 ENCLOSURE - DISP

- Installation: Complete
- Door interlocks: Complete
- Documentation: [redacted] Documentation – comment as per IQP 1178 29
- Drawings: Complete
- Utilities: Complete
- Maintenance: Complete
- Materials of construction: Complete
- Test Instrumentation: Complete
- Attachments: Complete

Qualitative Data – Code Sheet

B14.

Date : 7 November 2002 **Ref** : 1216ln1_djm

Subject : **Central Core – Issues, 7/11/02, 16:30**

Daily status meeting, 1:30 pm, [redacted] office.

Summary

The original programme indicated that all construction would be complete by 4/11/02. This is clearly not the case (as detailed below) and the area is still a building site. The plan was to have several contractors working in parallel this week to commission and validate the equipment and software. Not all actions have been completed due to the issues below. In several cases, contractor's availability has to be renegotiated and we cannot give a firm date until this has been completed.

The most critical task at the moment is the floor in the effervescent kitting area. Any "dirty" work in this area must be timed with the HVAC balancing which in turn affects the downflow booth balancing.

The delivery of the glue for floor welding is also critical and there is no further information on this.

30

B15.

Test Function 6 – Independent Room Pressure Differential tests

- No additional comment

Test Function 7 – Air Temperature tests

- No additional comment

88

Test Function 8 – Airflow distribution tests

- Video recorded smoke pencil/generator testing required.

Test Function 9 – Air particulate quality tests

- Particulate test section required.

18

Draft Operational Qualification protocol (issued by [redacted] during meeting)

- In addition to those OQ test above additional tests will be required for those critical parameters that have alarms associated with them i.e. pressure and humidity.
- We suggest that individual IQ and OQ documents for HVAC systems 04/01 and 04/02 are prepared, rather than one document covering construction zone 8. Critical components and equipment are not included in HVAC system 04/03 — IS THIS OK

[redacted] now needs to embrace all of the comments enclosed in this memo and transpose them into the HVAC system 04/01 and 04/02 OQ protocols.

Regards

Qualitative Data – Code Sheet

B16.

To	:	[redacted]	**cc**	:
Date	:	29 October 2002	**Ref**	:
Subject	:	**HVAC OQ Validation Protocols – Construction Zone 8**		

Dave

[redacted] and I have reviewed the validation documentation supplied by [redacted]s and have the following comments.

Draft of proposed Operational Qualification (OQ) test functions (prepared b[redacted] 16/10/02)

Test Function 1 – Standard Operating Procedure Identification

- WI should read Work Instruction (WI).
- SOP and Work Instruction Data will need to be supplied to [redacted]s to enable protocol preparation.

Test Function 2 - System Calibration Verification

- Section will need to include all critical instruments. The critical instrument list (that Dave [redacted] requires) should provide the foundation for this section.

Test Function 3 - Equipment Maintenance File review

- We are uncertain to the need for a second maintenance section. The maintenance section in the IQ appears to request the same information to that presented in the OQ. Can we eliminate this section from the OQ?

Test Function 4 - DOP HEPA filter integrity / Leak Testing

18

- Take out BS AND 209 E References - both were superseded in November 2001. For new facilities EN ISO 12644-1 and 2 should be applied.
- Review test procedure with regard to new legislation.

88

Test Function 5 – Filter face velocity, air volume and air change rate tests.

- Take out air velocity test – impractical to measure!
- There was no air volume or air change rate procedure in document provided for review.
- Testing procedure should refer to a recognised working standard (for example CIBSE/ASHRAE/NEBB etc).

Qualitative Data – Code Sheet

B17.

Date	:	29 October 200229 October 2002	**Ref**	:	1216lo20_djm
Subject	:	**Validation Documents**			

Dear [redacted]

In response to your Email, perhaps it would be better if we arranged a meeting to discuss the issues as we need an agreed way ahead, initially to effectively validate the HVAC systems and then the remainder of the project. Could you please let me know when you are available and I will arrange for [redacted] and Mike [redacted]) to attend. We need to discuss the following:

HVAC

In terms of the HVAC, product quality is protected by means of pressure differentials, air flows, air change rates and HEPA filtration. The design of the HVAC is fairly simplistic, with central controls and a heavy reliance on Pressure Control Dampers, Volume Control Dampers and Laminar Flow Units. You are right that you have "no design information..... to impart", but the implication of your design are that these components are critical to the commissioning and operation of the systems, and as such need to be fully documented.

The starting point for the documentation is the tag number, some of which are currently missing from the construction drawings as previously notified. We saw this as being the designer's deficit.

87

Whilst Construction Zone 8 is a fairly low pharmaceutical classification, you have included HEPA filtration and each HEPA filter needs full documentation. We also need to have the unique and specific test certification, as supplied by the manufacturers for each filter cell. We do not need tag identity for each cell, but we do need a tag identity for each filter housing

Qualitative Data – Code Sheet

B18.

Purified water

There are also issues with the purified water system which seems to involve three distinct extensions: Zone 8 Bin wash and Dispensary, Zone 11 [redacted] Glatt Vessels and the [redacted]e loop. If we are to use any of these loops before completion of all three elements, we must have clear segregation of drawings, testing and commissioning. The design needs to consider how we avoid multiple sanitisation events if this is possible.

Drawings

We do not want to renumber any drawings, what was discussed with your [redacted] was a "stamp" or AutoCAD drawing box that could be added or appended to the drawings and we had thought Mike was going to come up with a proposal for this. The "stamp" or electronic drawing box needing to be attached to the "As built" or "Red Lined Drawings".

We do need to ensure that someone, other than the contractor, is checking and certifying all red lined and or "as built" drawings are correct. [redacted]

86

We are desperately struggling to complete this validation on time and without the required information, the central core facilities cannot be used. I have sent a memo to [redacted] with detailed lists of the information we require but I also need your help to complete the validation within what is now a very tight schedule. Please contact me to arrange a meeting.

Kind regards,

[redacted]
Validation Manager

B19.

09/04/2003 10:07:00

This is mainly a reminder to myself that there are some approval pages in
the VSP2 documents for the central core which are not signed.

We can cross at the witnessed bit as we are only approving, not witnessing, but the some of the pages which have been copied for the OQ
attachments are not signed. We need to rectify this ASAP

Dave

86

Qualitative Data – Code Sheet

B20.

Check matrix for completion of the central core validation

Fabric and environment 19

HVAC systems		DQ	IQ	OQ	PQ
HVAC system 04/01, Zone 8, Dispensary		3	3	3	3
HVAC system 04/02, Zone 8, IBC washer and area		3	3	3	3
HVAC system 04/03, Zone 8, Dispensary General		3	3	3	3
Compressed Air, Zone 8, Central core (Non Process)		x	x	x	x
Purified Water, Zone 8, IBC washer and area		3	3	3	3
Vacuum, Zone 8, Dispensary (for cleaning)		x	x	x	3
Dust extraction		x	x	x	3

B21.

Diary Memo – Note

Design Review documentation produced and executed post iq,oq in November, december 2003.

51 68

Qualitative Data – Code Sheet

B22. Client Audit January 2003.

Observations Existing Facility	Root Cause Existing Facility	Planned Corrections New Facility	Recommendations New Facility	January 2003 Assessment
• Blocked filters	• Air flows not correct • Dispensing operation generates too much powder (link to break up of aggregates and agglomerates) • Wrong filter type?		• Review (operations, engineering and quality) to determine actual root cause and correct design/working practices/maintenance	• Gauges are declared not to be calibrated • WI 09.014 issue N°1: preparation of down flow booth 4.11 and 4.12 require checking
•	•	•	•	• scale: calibration label with no expiration date
• Sara door left open	• Reliability of door opening • Door is on main access/exit to the whole area and is in constant use	• New facility design improves flows and separates out material/personnel flow where needed • Different design/make of door used	• Introduce controls prevent unauthorised locking open of automatic doors • Ensure doors are included on maintenance schedule	• MAL interlocked, change during qualification, way of working to be precise • PAL not interlocked but "alarmed" • Liquid dispensary PAL is an emergency exit
• Poor/crossed flows of materials and people • Inadequate segregation between warehouse and dispensary area • No airlocks for people or materials	• Facility design	• Facility designed to eliminate issue	• Crossed material flow exists for the liquid dispensary; ensure procedural controls	• No air-lock between zone 1 and 2 • Medical centre located in this area: gowning? • No pressure gauge for MAL and PAL • No segregation in PAL between the two zones • Doors with glasses, modesty? • WI 09.021 issue N°1 : Liquids weighing dispensary • Dispensed material has to go through pallet change area, no special caution
				• No cupboards: office, change pallet area,…
				• No signage: location, status,…
				• Kitting area not sued as planned • Some location not accessible
				• "Palamatic" lift doesn't work

45

Qualitative Data – Code Sheet
B22. Continued
Qualification

Observations Existing Facility	Root Cause Existing Facility	Planned Corrections New Facility	Recommendations New Facility	January 2005 Assessment
				• No systemic approach to prove that every thing is included
				• Date of signature management: Don't follow the order of the sheet minor URS booth accepted by supplier before signed by HSE OQR approved before IQR
			30	• Problem of air flow influence on bench scale
				• PXXXX/06/A issue 2: what is the reason? Why it is not accepted by supplier?
				• What is the link between I3 containment, URS and FAT, and air flow parameters for others tests
				• Booth: gauges for indication only lights 824.5LUX instead of 500 motor speed proved by air flow
			48	• IA-1178-1 Instrument assessment HVAC system Location hand written in red on a copy , official drawing?
				• IQR-1178-1 HVAC system serving dispensary Area in Central Core Temperature probes not able to be calibrated
				• IQR-1214-1 Environmental monitoring Temperature probes to be replaced
				• Change of way of working for MAL to be explained

Manually Coded Data – Case Study C

Qualitative Data – Code Sheet

C1.

CI1 Newsletter – September 2001

GMP Upgrade Project

A GMP Upgrade Project at XXXX has been officially launched. The aims of the project are to upgrade the practices at XXXX to meet the ever demanding needs of the regulatory authorities. GMP stands for **Good Manufacturing Practice**, and encompasses all activities related to manufacture, packaging, testing and distribution of pharmaceutical p 40

The project is led by Quality Assurance, but will impact on all areas of the factory. It is essential that the project is successful, not only to achieve FDA approval for Product x, but also to meet continually escalating standards expected by the Medicines Control Agency and other European authorities. Full support for the project has been given by the Company's Industrial Affairs group in Paris, and CI1 US Quality Department will provide advice and support to help XXXX toward 41 42

A multi-functional team has been established and is already working on ways to improve basic aspects of GMP including labelling and documentation. The next phase will be to assess and simplify the system of documented procedures on site (Standard Operating Procedures or SOPs). These procedures cover the operational processes required at XXXX and in future they will be governed by Quality Policies contained in the XXXX Quality Manual. The policies will be based on Corporate Directives and Guidelines, and also the European Good Manufacturing Practices and the US CFRs (Code of Federal Regulations).

The project involves everybody at XXXX, with many sub-teams being established to assess current practices and to modify them to achieve the required GMP standards and where possible simplify the practices. These sub-teams will help prepare the revised Work Instructions which will provide clear and simple instructions for use by the work force when carrying out all GMP related activities. Work Instructions will link directly with the SOPs, which will be an overview of the processes required to manufacture product to the required quality. 40

The impact on the site will be significant, particularly as the project will be running side by side with the refurbishment of the site. However the determination, enthusiasm and expertise of the XXXX work force, and the support from France and the US, will certainly contribute to the success of the project.

Qualitative Data – Code Sheet

C2

GMP Upgrade Project

C11 Newsletter – September 2002

GMP Upgrade Project

The activities of the GMP Upgrade Project are intrinsically linked with those of Project XXXX (Construction project). All activities are controlled by a common (master) plan, ensuring delivery of procedures and training in time for operational launch of 82 s.

There remains a tremendous amount of work and effort to prepare and fully implement the new and improved quality system. Nevertheless, the concerted efforts of the XXXX work force will ensure a stable system will be achieved by the end of 2003. In tandem, we will be preparing the sNDA for Product X, and then we will invite the FDA to in 41 site!

C3.

GMP Upgrade Project

Article for Newsletter – April 2002

GMP Upgrade Project

- Integrated plan of Project XXXX(Construction Project) and GMP Upgrade Project now approved – it is called the XXXX GMP P 41 46

C4.

Meeting held 13th October 2003

Manuals

1.1. OL will look into the possibility of the OQ documentation being available with the manuals.

1.2. CO/CP will list specific shortcomings relating to existing manuals for discussion/review with Contractor 2. 73 30

Qualitative Data – Code Sheet

C5.

System	URS	Validation	Protocol				Report				Comment
			DQ	IQ	OQ	PQ	DQ	IQ	OQ	PQ	
HVAC											
Supply and Extract System 06/03	0960-1		✓	✓	✓	✓	✓	✓	✓	✓	Protocol to be written by VSP2 Validation Consultants
Existing Manufacturing Corridor (AC1, AC2)		0935		✓	✓			✓	✓		Protocol to ensure existing rooms maintain correct pressures during construction of new suites. Document to be issued for each phase of construction.
				19			63		60		
									29		
Enclosure											
Phase 1	0960-1	1238	✓	✓			✓	✓			Compression Suites 1, 2 and 3
Phase 2	0960-1		✓	✓			✓	✓			
Phase 3	0960-1		✓	✓			✓	✓			
Phase 4	0960-1		✓	✓			✓	✓			
Environmental Monitoring											
Phase 1	0960-1	1239	✓	✓	✓	✓	✓	✓	✓	✓	Compression Suites 1, 2 and 3
Phase 2	0960-1		✓	✓	✓	✓	✓	✓	✓	✓	
Phase 3	0960-1		✓	✓	✓	✓	✓	✓	✓	✓	
Phase 4	0960-1		✓	✓	✓	✓	✓	✓	✓	✓	

Qualitative Data – Code Sheet

C6. Validation Plan

83

In order to meet potential changes to the C11 product portfolio, production patterns and to comply with the anticipated regulatory requirements for the manufacture of pharmaceutical products, C11 is upgrading and consolidating manufacturing facilities at XXXX. The upgrade is named "The XXXX Project" and the requirements of the design are detailed in the approved User Requirement Specification (URS-09-1).

The XXXX Manufacturing Centre validation policy, strategy and plans are currently described in the site Validation Master Plan (VMP-08).

The validation approach for the XXXX Project is described in the Project XXX Validation Master Plan (VMP-09-1), the purpose of which is to present an overall plan for the validation of facilities and equipment (including computerized systems) which need to be addressed in order to ensure a fully validated facility.

This purpose of this specific XXXX Project and Equipment Validation Plan is to present in a single coherent document, the plan for those activities which when completed will result in the modifications to the tablet manufacture (compression) department being confirmed and documented as suitable for their intended purpose.

The compression area will be progressively reworked to provide 10 rooms, four of which will have low humidity control capabilities. Each room will have MAL and PAL facilities. Space will be available for two further rooms. The rooms will be supplied with material from the feeder floor above. All of the above facilities are located within the existing building.

87

Compression rooms feed stations are located on the first flo[illegible]hers are docked onto the feed station and blended material is passed into a hopper on the compression machines. Compressed tablets are de-dusted and loaded into smaller IBC and transferred to the Bulk Tablets Store.

The compression department layout has been developed to recognize three environment zones as follows:

- Zone 1

Areas where protection from the external environment is required such as offices outside production areas, warehouse, technical areas etc.

- Zone 2 (Manufacture)

Areas within manufacturing where product is not exposed, such as manufacturing corridors

- Zone 3

Areas where product is exposed, such as compression cubicles.

41

Qualitative Data – Code Sheet

C7.

40

	Compression Cubicle 1	**Compression Cubicle 2** 63	**Compression Cubicle 3**
Phase 1	IQP-1187-1 (HVAC - Central plant).	IQP-1187-1 (HVAC - Central plant).	IQP-1187-1 (HVAC - Central plant).
	OQP- 1187-1 (HVAC)	OQP-1279-1 (HVAC)	OQP-1280-1 (HVAC)
	IQP-1238-1 (Enclosure)	IQP-1269-1 (Enclosure)	IQP-1270-1 (Enclosure)
	IQP-1239-1 (Environmental Monitoring)	IQP-1271-1 (Environmental Monitoring)	IQP-1272-1 (Environmental Monitoring)
	OQP-1239-1 (Environmental Monitoring)	OQP-1271-1 (Environmental Monitoring)	OQP-1272-1 (Environmental Monitoring)

C8.

31/03/03
Re: Compression Phase 1
John and Paul - will you have time to see Gary this morning and explain what is involved? Has Gary met Tom?
Does Tom know what's involved?

52

After all the delays so far, we don't want validation delays to hold up the first move.

21

Re: tagging. I haven't been able to sort this out yet and it will be better if we do it ourselves like last time. I will try to ensure it doesn't happen again and that next time, all the instruments are tagged.

C9.

32

09/04/2003
Also, Hugh will need to borrow the video camera for his smoke tests. Do you know where it is and can you give him a bit of training?

18

Dave

26

C10.

31/03/2003 08:24:05

87

Thanks Paul.

One more thing - we won't be able to get access to the rooms until the temperature and humidity monitoring is complete.
Should be sometime today.
I'll let you know.

Dave

C11.

28/03/2003 14:16
We now have a full week to complete the GMP enclosure and environmental monitoring protocols for compression room 1, 2 and 3.

49

Qualitative Data – Code Sheet

C12.

19/03/2003 15:47
Due to the collection of issues described below, it is necessary to postpone the movement of the first press into new compression room 2 until 31st March as the room will not be ready on the 24th as planned. 48

It is essential to minimize the downtime of the press and we don't want it moved if it means it could be off-line for more than the allocated week.

The issues are as follows:

There have been problems with the steam supply from the energy centre and i'm told the supply is being turned off tonight for some re-work to the pipework by the contractors. The supply will not be back on until Friday which too late to complete the IQ/OQ of the HVAC and environmental monitoring systems before Monday. The lack of steam also affects the commissioning of the environmental monitoring systems as described below. 55

Invensys have been given no formal instruction to re-wire the chart recorder to our requirements as discussed at the Validation/Engineering meeting on Monday. Temperature and humidity probes are in place but are not configured as we required as per the memo from Metrology. Invensys cannot commission this equipment until Monday/Tuesday next week as they need all utilities to be available, including steam. 5 87

Pressure panels are not powered up, the alarms are not set on transmitters and so have not been tested. The mismatch between housing and covers on chart recorders is still to be rectified. 22

The flaps between the compression room and the MAL are still not fitted correctly and may allow the ingress of too much "non-dehumidifed" air. The flaps should have GMP "rubber" flanges to form a better seal. 21

In the plant room, the pressure transmitters and the Magnehelic gauges on the Munters units are in place but are not connected. Also there is a Magnehelic gauge on the floor, which I think has "fallen off" AHU 06/03 supply (across the HEPA). 07

This delay to the first move also pushes back the subsequent moves. Press to room 1 now on 7/4/03 and to room 3 on 14/4/03.

Please contact me if you require further information or clarification.

Dave

Qualitative Data – Code Sheet

C13.

18/03/2003 08:50:01

Ian

Chart Recorders
Following our Validation meeting yesterday (Monday) and with reference to the e-mail I sent out about chart recorders (attached below), Dave XXXX (C11Validation Dept.) has agreed that the recorder and chassis serial numbers should match in all installations to prevent possible queries during future quality audits of the facility by FDA etc. The problem has already been identified in the Warehouse and in Zone 6 chart recorders and we'll need to do a survey of all the other recorders fitted so far and assess the situation from there.

73

05

Calibrated Temperature Sensors
I've had 12 of the Rotronic sensors calibrated. Six are for the warehouse and the other six are for putting in temperature critical areas. The most pressing installation presently is that of TX06/22 - the compression area general extract temperature sensor. Is it possible for this sensor to be fitted before this Thursday (20th March) to allow validation work to commence?

Regards

Dave XXXXX
Instrument Calibration Engineer

Qualitative Data – Code Sheet

C14.

Minutes from meeting on 10/3/03: 87 88

1. Approval of record drawings for central core and compression phase 1. Drawings not to be approved until they are correct (ie when outstanding items (PDI/switches) are fitted. .

Mike XXXX (C2) to chase up delivery date for items. 57 67

2. Chart recorders for compression area - channels split between different recorders.

Dave XXXX/Peter XXXX to produce detail of requirements by Wednesday 12th, am. Record drawings to be changed accordingly - Owen to take to Services Engineer on Thursday 13th.

3. Compression phase 1 validation:
Steam on but possible issue with condensate. Munters in 11th/12th.
Panels to be cut today.
However, changes to drawings, installation of PDIs etc and changes to chart recorder will cause delays. Hope to start validation Tuesday 18th March and have complete as much as possible (without the press) in room 1 before the first press move on 24th March. IQ to be approved (with Owen, 10/3/03). OQ to be finalised. 63

4. Blanking off of compression phase 2a ductwork - method statement required etc. Not discussed, insufficient time. 03

Next meeting, Monday, 17th March, 3:30. Engineering Conference Room.

Dave

Qualitative Data – Code Sheet

C15.

Yes, I have a few items -

1. Still awaiting dispensary record drawings. 87

2. Chart recorders for compression area - channels split between different recorders.

3. Blanking off of compression phase 2a ductwork - method statement required etc.

4. Possible compression phase 1 problems – Commissioning engineer to complete air balance, Invensys still to complete controls commissioning and addition of PDS's, PDI's and cabling back to BMS (sorry BAS).

Dave XXXX
10/03/2003 13:21

C16.

06/03/2003 11:48 AM
Subject: Chart Recorders

Dave 03

After a recent discussion with Ron XXXX of Invensys it appears that only Compression suite 1 HVAC detectors are connected to Chart Recorder CR06/01. This means that detectors for compression rooms 2 and 3 go back to chart recorder no. 2. As a result of this information Services Engineers HVAC schematic diagrams for Compression phase 1 will require modification and also hvac/monitoring protocols will need updating.

See attached word document for details of chart recorders 1,2 and 3.

Regards

Qualitative Data – Code Sheet

C17.

04/03/2003 10:47:52

Mike
The current situation with the (critical) BMS temperature sensors is as follows.

Invensys have bought some new sensors from Rotronic (a box full! - including 6 specifically for the warehouse area). Ian XXXX has dropped the sensors off in Metrology for us to calibrate - although they do come with a one-point factory calibration certificate. The sensors are to be calibrated (ideally) at 10, 20 and 30 Deg C but since we no longer have our old incubator in Metrology (since it wouldn't fit in the new department) I can only calibrate them at around 25C and 30 C which is obviously no good.

87

We have a few options.
If I can get access to our old incubator we could calibrate them at 19 (nineteen is as low as this unit will go), 25 and 30 Deg - which is perhaps acceptable until we buy some sort of environmental chamber to perform such calibrations?
we get them done externally at 10, 20 and 30 Deg C until we get the new chamber (I'm getting a price from a local firm)
we wait until we buy a new chamber then do them in there (could be ages? - if ever!)
accept the factory calibration certificate for the first calibration then do future calibrations in our new chamber (not normal procedure)

How many calibrated temperature sensors do you reckon we need ASAP? I'm assuming the 6 warehouse ones are required ASAP but how many do we need to complete the Central Core, Compression, ESP(?) validations

Regards

Qualitative Data – Code Sheet

C18.

03/03/2003 17:11:37

To: C2
cc:
Subject: Phase 1 Compression Drawings

Mike, I've received the signed record drawings from Services Engineer for compression phase 1.

I assume you also have a copy.

Please note that the covering letter contains an instruction for C2 to fit PDIs and pressure switches across the dehumidifier HEPAs.

Could you please let me know when these have been installed so I can confirm that the drawings are correct.

Thanks,

87

Dave, QA validation manager

Qualitative Data – Code Sheet

C19.

03/03/2003 08:58:36

Hugh
Thanks for the protocols, comment for each are listed below.
IQ – Mike has looked through the first 8 pages and has the following feedback. Please ensure that the rest of the document is fully reviewed prior to issue for approval

73

Equipment Installation
1. Temperature Sensor - inlet air , manufacturer is Invensys not Satchwell.
2. Frost stat model is TCL 1603 not DDT 1603.
3. Pressure differential indicator - Panel filters, range is 0 to 250 Pa not 0 to 500 Pa.
4. Pressure differential switch - Panel filters, model is SPA 1401 not SPA 1402. Same comments for PDS 06/22.
5.Pressure differential switch across the supply fan, model is SPA 1401 not SPA 14/02 and range is 0.2 to 3mBar not 1to 10 mBar.
6. Rotoflow device, supply fan flowrate controller, model is DDP 4203 not DDP 42/03.Spec number is !22-4-203 not 122-4-403.
7. Pressure differential switch - high efficiency filters, manufacturer is Satchwell not Dwyer, model is SPA 1402 not Magnahelic (Magnehelic?) and range is 1 to 10 mBar.
8. A number of filter efficiency classifications are still incorrectly stated i.e G7

OQ

76

Approvals should be the same as for the IQ
Objective - refers to an IQ document rather than OQ
Document continues to switch between "room" and "suite" reference
Monitoring protocol cross reference for suite 1 is 1239. For suite 2, the reference is 1271 and suite 3, 1272
Test number on page 21 does not follow format of document
Header text wanders - refer to page 35 for an example
Page 41 - put a space between the table and the next test reference
Footers still require sorting - the "reviewed by" text is only required on the last page of every test section

Qualitative Data – Code Sheet

C20.

28/02/2003 10:24

Subject: revised protocols

73

John

Please find attached our revised protocols for the compression area.

Regards

Stuart XXXX
- 28.02.03 OQP1187 Draft.doc
- IQP Compression 1,2,3 (28-2).doc

76

C21.

27/02/2003 10:47:40

There are three issues we need to resolve before we can begin the validation of the HVAC systems in phase 1 compression. The start of this work is scheduled for 7th March and is dependent on the steam and Munters (dehumidification sytem).

The through floor feeds need to be properly plugged (the "dustbin lids" do not provide a good seal). We suggest using expandable drain plugs (in the top), or neoprene bungs (again, in the top) or some form of Tupperware type lid (on the bottom).

21

The extract grilles need to be removable for cleaning. I thought the plan was to fit some finger tight screws so that they could be removed. These have not yet been fitted. As I have said before, it would be advisable to fir some type of coarse filter behind the grille.

The conveyor needs to be in place, the hole needs to be cut in the panel, and the "flap" needs to be fitted.

21

On a separate issue, we have still not received the record drawings for the central core and we don't have signed off drawings for compression phase 1 (as we agreed with the Services Engineer last week).

21

Dave

Qualitative Data – Code Sheet

C22.

20/02/2003 09:20:51

Should be okay.

Mike, as part of the list, non-critical instruments have to be given a justification for being so and attached to each, can we think on about this and about appropriate wording (and as such the Cenral core!).

27

48

Regards

Paul XXXXXX Calibration Cl1

C23.

14/02/2003 10:46
Subject: Compression

Mike/Jim,

67

With reference to the dehumidifiers on compression (DH 06/03, 04, 05 and 06) would you please carry out the following:-

63

1). Install a magnehelic gauge to the regen air filter to operate in parallel with the pressure switch. The gauge needs to be a Dwyer series 2000 with a range in the order of 0 - 500 Pa. Munters state that this gauge has been supplied loose and is usually fitted upon commissioning.

70

2). Install a Pressure differential switch and a magnehelic gauge across the HEPA filters on the process air side. Gauge and range as above. This gauge needs to be monitored by the BMS.

3). The differential pressure switch associated with the process filter (G7) needs to be removed. This is part of the dehumidifier and will have to be done by Munters.

4). The G7 filter on the process air must be removed.

We are modifying the drawings and they will be issued tonight.

Mick XXXXXXXXXX

Services Engineer

Qualitative Data – Code Sheet

C24.

14/02/2003 10:51 PM

Owen,

Having being all round this C2 site with Mike, we couldn't see how you gain access to these probes from anywhere safely. 03

Could we have a walk round with you?

Regards

Paul XXXX.

Following a survey of the Compression phase 1 HVAC system with Metrology and Chris XXXX, it was unclear how we could gain access to the humidity probes that are connected to the extract ductwork from each of the humidity controlled compression booths.

Do you know how to get access to these detectors as they are critical instruments and require calibration? The only possible access that Paul and myself could identify was from through the wall at the back of the service area adjacent to the road. However, the opening was quite small and partially filled by pipework and it appeared that it would be very hazardous to climb through.

Any ideas on how we could overcome this problem?

Thanks
Mike

C25.

Compression Phase 1 – Memo MARCH 03

- Validation engineer had very little or no validation experience.
- Validation of three tablet compression rooms 1, 2, and 3.
- Room 2 came on line first and was therefore validated independently of 1 and 3.
- Initial problems relating to the quality of the validation documentation supplied by the hvac validation engineer.

26 86

APPENDIX C - Validation Questionnaire (Initial)

Please tick one response in relation to the following statements.

Key: SA Strongly agree A Agree N Neither agree or disagree D Disagree SD Strongly disagree

	SA	A	N	D	SD
1.The process of building/facility validation is seen as expensive.	☐	☐	☐	☐	☐
2.The process of validation is seen as complex to implement.	☐	☐	☐	☐	☐
3.Validation is primarily seen as a task undertaken for the sole purpose of opening up business markets.	☐	☐	☐	☐	☐
4.The variables of value and quality are increased by the process.	☐	☐	☐	☐	☐
5.Those involved in the process are uninformed and unclear of the project objectives.	☐	☐	☐	☐	☐
6.Validation may be seen as an expensive project task sitting between the contractors final payment and the facilities owners first run of product.	☐	☐	☐	☐	☐
7.The timing of the implementation is crucial to the success of the whole construction project.	☐	☐	☐	☐	☐
8.A validation project duration is difficult to estimate.	☐	☐	☐	☐	☐
9.Regulation s Governing the installation of clean systems are too stringent	☐	☐	☐	☐	☐
10.Validation adds to the overall project duration.	☐	☐	☐	☐	☐
11.Project validation should not be necessary if commissioning is carried out.	☐	☐	☐	☐	☐
12.The installer/supplier of systems and facilities displays a lack of understanding of his validation responsibilities in relation to the project.	☐	☐	☐	☐	☐
13.Projects run more smoothly when an integrated approach is adopted i.e all those involved with any aspect of the project have an input into the project, including validation at an early stage	☐	☐	☐	☐	☐
14.Validation should be carried out at the final stages of a project to allow the installation work to proceed without interruption.	☐	☐	☐	☐	☐
15.Validation is generally better left to the organisations who design/install because they have a more detailed understanding of the system.	☐	☐	☐	☐	☐
16.In-house (client) validation teams provide a more thorough execution of testing documentation.	☐	☐	☐	☐	☐
17.Validation is a new area of quality assurance that does not have clear objectives.	☐	☐	☐	☐	☐
18. Validation of a clean facility is worthless if a system of maintenance is not in place to ensure that performance levels are maintained.	☐	☐	☐	☐	☐
19.A validation budget exceeding 15 % of total project cost is excessive	☐	☐	☐	☐	☐
20.IQ and OQ work should be checked by engineers and constructors and not QA/QC personnel.	☐	☐	☐	☐	☐
21. If an installer is testing a system during installation it is wasteful to repeat the tests as part of a validation exercise.	☐	☐	☐	☐	☐
22. Most commissioning documentation is of low quality and not suitable for validation purposes	☐	☐	☐	☐	☐

23. A well written commissioning document could be used in lieu of a validation document	☐	☐	☐	☐	☐
24. Commissioning should be used to qualify non-critical systems as it is likely that good engineering practice will ensure a properly installed plant or system.	☐	☐	☐	☐	☐

Should you have any comments please write in the space below.

Pharmaceutical Facility Construction and Validation Questionnaire (Final)

What is your job title? _____

How many years have you been involved in the Construction or Pharmaceutical industry?	0 – 5 ☐	5 – 10 ☐	10 – 20 ☐	20 – 30 ☐	30 – 40 ☐	50+ ☐
How many years have you been involved in the validation of pharmaceutical facilities?	0 - 5 ☐	5 – 10 ☐	10 – 15 ☐	15 – 20 ☐	30+ ☐	

Please tick one response in relation to the following statements.

Key: **SA Strongly agree** **A Agree** **N Neither agree or disagree** **D Disagree** **SD Strongly disagree**

Part 1	**SA**	**A**	**N**	**D**	**SD**
1. The design/construction team are rarely involved with the clients QA team early in the project.	☐	☐	☐	☐	☐
2. The validation of a pharmaceutical facility is:-					
- Only required if the pharmaceutical client asks for it.	☐	☐	☐	☐	☐
- An essential requirement for regulatory compliance.	☐	☐	☐	☐	☐
- Complex to implement.	☐	☐	☐	☐	☐
- Expensive to implement.	☐	☐	☐	☐	☐
3. Facility validation duration -					
- Is difficult to estimate.	☐	☐	☐	☐	☐
- Adds to overall project duration.	☐	☐	☐	☐	☐
4. Facility validation cost is:-					
- Difficult to estimate.	☐	☐	☐	☐	☐
- Difficult to control	☐	☐	☐	☐	☐
5. The calculation of facility validation cost is based on:-					
- Past experience.	☐	☐	☐	☐	☐
- Use of a planning matrix where all possible validation activities are identified.	☐	☐	☐	☐	☐
- A specialist subcontractors quotation.	☐	☐	☐	☐	☐
- A budget percentage sum.	☐	☐	☐	☐	☐
- The time slot available for commissioning at the end of the project.	☐	☐	☐	☐	☐

	SA	A	N	D	SD
6. As a percentage of the overall facility Construction, validation costs are normally:-					
- Below 5%	☐	☐	☐	☐	☐
- Between 5% and 10 %	☐	☐	☐	☐	☐
- Between 10% and 15%	☐	☐	☐	☐	☐
- Between 15% and 20%	☐	☐	☐	☐	☐
- Above 20%	☐	☐	☐	☐	☐
7. Which areas of a pharmaceutical manufacturing site require validation:-					
- offices	☐	☐	☐	☐	☐
- Site restaurants	☐	☐	☐	☐	☐
- Product manufacturing areas	☐	☐	☐	☐	☐
- Product packaging areas	☐	☐	☐	☐	☐
- General circulatory spaces	☐	☐	☐	☐	☐
- Dispensaries	☐	☐	☐	☐	☐
- Warehouses	☐	☐	☐	☐	☐
8. With reference to Production/packaging product contact areas which of the following require validation:-					
- Facility internal construction materials	☐	☐	☐	☐	☐
- HVAC systems	☐	☐	☐	☐	☐
- Room monitoring systems	☐	☐	☐	☐	☐
- Purified Water systems	☐	☐	☐	☐	☐
- General indirect utility systems	☐	☐	☐	☐	☐
- Product contact gases	☐	☐	☐	☐	☐
9. Regulations Governing the validation of pharmaceutical facilities are:-					
- Too stringent.	☐	☐	☐	☐	☐
- Difficult to understand.	☐	☐	☐	☐	☐
- Too general and not detailed enough.	☐	☐	☐	☐	☐
- Vastly different from country to country.	☐	☐	☐	☐	☐
- Difficult to obtain	☐	☐	☐	☐	☐
10. A validated facility is considered compliant when it:-					
- Fulfils the requirements of the initial design.	☐	☐	☐	☐	☐
- Is completed on time and at no additional cost.	☐	☐	☐	☐	☐
- Satisfies the client.	☐	☐	☐	☐	☐
- Satisfies regulatory inspection.	☐	☐	☐	☐	☐
11. Validation normally starts at the initial design stages of a facility Project.	☐	☐	☐	☐	☐

	SA	A	N	D	SD
12. Validation normally starts when all construction activities are complete as to allow the installation work to proceed without interruption.	☐	☐	☐	☐	☐
13. The timing of the implementation is crucial to the success of the whole construction project.	☐	☐	☐	☐	☐
14. Project validation should not be necessary if high quality commissioning is carried out.	☐	☐	☐	☐	☐
15. A well written commissioning document could be used in lieu of a validation document.	☐	☐	☐	☐	☐
16. Facility validation should be left to the pharmaceutical client.	☐	☐	☐	☐	☐
17. Validation is generally better left to the organisations who design/install as they have a more detailed understanding of the systems.	☐	☐	☐	☐	☐
18. Most construction companies are not sufficiently experienced to complete the validation of a facility i.e. writing protocols, carrying out tests and reporting outcomes.	☐	☐	☐	☐	☐
19. If an installer is testing a system during installation it is wasteful to repeat the tests as part of a validation exercise.	☐	☐	☐	☐	☐
20. Commissioning should be used to qualify non-critical systems as it is likely that good engineering practice will ensure a properly installed plant or system.	☐	☐	☐	☐	☐
21. Projects run more smoothly when an integrated/partnering approach is adopted. i.e all those involved with any aspect of the project have an input into the project, including validation at an early stage.	☐	☐	☐	☐	☐
22. Validation is a new area of quality assurance that does not have clear industry guidelines.	☐	☐	☐	☐	☐
23. Validation of a facility is worthless unless a system of continued maintenance is in place to ensure that performance levels are within specification.	☐	☐	☐	☐	☐
24. During the facility validation there are usually sufficient systems in place to allow feedback and corrective action if something has been incorrectly designed, installed or commissioned.	☐	☐	☐	☐	☐

Part 2
The PHARMACEUTICAL INDUSTRY is:-

	SA	A	N	D	SD
25. Flexible.	☐	☐	☐	☐	☐
26. Profit focused.	☐	☐	☐	☐	☐
27. Contractual.	☐	☐	☐	☐	☐
28. Insular.	☐	☐	☐	☐	☐
29. Efficient.	☐	☐	☐	☐	☐
30. Research lead.	☐	☐	☐	☐	☐
31. Highly regulated.	☐	☐	☐	☐	☐
32. Adequately resourced.	☐	☐	☐	☐	☐
33. Proactive.	☐	☐	☐	☐	☐
34. Highly technological.	☐	☐	☐	☐	☐
Those employed in the PHARMACEUTICAL INDUSTRY :-					
35. Have low job related stress.	☐	☐	☐	☐	☐
36. Have high job satisfaction.	☐	☐	☐	☐	☐
37. Receive good pay/employment packages.	☐	☐	☐	☐	☐
38. Are highly motivated.	☐	☐	☐	☐	☐
39. Have a comfortable and safe working environment.	☐	☐	☐	☐	☐
40. Receive adequate job focussed training	☐	☐	☐	☐	☐
41. Generally work in one site/office location and seldom travel for work.	☐	☐	☐	☐	☐
42. Feel that their job offers sufficient challenges.	☐	☐	☐	☐	☐
The CONSTRUCTION INDUSTRY is:-					
43. Flexible.	☐	☐	☐	☐	☐
44. Profit focused.	☐	☐	☐	☐	☐
45. Contractual.	☐	☐	☐	☐	☐
46. Insular.	☐	☐	☐	☐	☐
47. Efficient.	☐	☐	☐	☐	☐
48. Research lead.	☐	☐	☐	☐	☐
49. Highly regulated.	☐	☐	☐	☐	☐
50. Adequately resourced.	☐	☐	☐	☐	☐
51. Proactive.	☐	☐	☐	☐	☐
52. Highly technological.	☐	☐	☐	☐	☐

Those employed in the CONSTRUCTION INDUSTRY :-

	SA	A	N	D	SD
53. Have low job related stress.	☐	☐	☐	☐	☐
54. Have high job satisfaction.	☐	☐	☐	☐	☐
55. Receive good pay/employment packages.	☐	☐	☐	☐	☐
56. Are highly motivated.	☐	☐	☐	☐	☐
57. Have a comfortable and safe working environment.	☐	☐	☐	☐	☐
58. Receive adequate job focussed training.	☐	☐	☐	☐	☐
59. Generally work in one site/office location and seldom travel for work.	☐	☐	☐	☐	☐
60. Feel that their job offers sufficient challenges.	☐	☐	☐	☐	☐

Should you have any comments please write in the space below.

Crosstabulations

Years involved in the construction or pharma industry

Job title			Frequency	Percent
const	Valid	10 - 20 years	7	63.6
		20 - 30 years	2	18.2
		30 - 40 years	2	18.2
		Total	11	100.0
pharma	Valid	0 - 5 years	2	8.7
		10 - 20 years	8	34.8
		20 - 30 years	10	43.5
		30 - 40 years	3	13.0
		Total	23	100.0

Years involved in the construction or pharma industry

Job title			Valid Percent	Cumulative Percent
const	Valid	10 - 20 years	63.6	63.6
		20 - 30 years	18.2	81.8
		30 - 40 years	18.2	100.0
		Total	100.0	
pharma	Valid	0 - 5 years	8.7	8.7
		10 - 20 years	34.8	43.5
		20 - 30 years	43.5	87.0
		30 - 40 years	13.0	100.0
		Total	100.0	

Years involved in validation

Job title			Frequency	Percent
const	Valid	0 - 5 years	3	27.3
		5 - 10 years	3	27.3
		10 - 15 years	4	36.4
		15 - 20 years	1	9.1
		Total	11	100.0
pharma	Valid	0 - 5 years	3	13.0
		5 - 10 years	11	47.8
		10 - 15 years	1	4.3
		15 - 20 years	8	34.8
		Total	23	100.0

Years involved in validation

Job title			Valid Percent	Cumulative Percent
const	Valid	0 - 5 years	27.3	27.3
		5 - 10 years	27.3	54.5
		10 - 15 years	36.4	90.9
		15 - 20 years	9.1	100.0
		Total	100.0	
pharma	Valid	0 - 5 years	13.0	13.0
		5 - 10 years	47.8	60.9
		10 - 15 years	4.3	65.2
		15 - 20 years	34.8	100.0
		Total	100.0	

Early involvement between construction and pharm groups

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	5	45.5	45.5	54.5
		D	4	36.4	36.4	90.9
		SD	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	12	52.2	52.2	52.2
		N	1	4.3	4.3	56.5
		D	7	30.4	30.4	87.0
		SD	3	13.0	13.0	100.0
		Total	23	100.0	100.0	

Validate if asked for by client

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	2	18.2	20.0	20.0
		A	2	18.2	20.0	40.0
		D	3	27.3	30.0	70.0
		SD	3	27.3	30.0	100.0
		Total	10	90.9	100.0	
	Missing	.0	1	9.1		
	Total		11	100.0		
pharma	Valid	SA	1	4.3	4.3	4.3
		N	1	4.3	4.3	8.7
		D	3	13.0	13.0	21.7
		SD	18	78.3	78.3	100.0
		Total	23	100.0	100.0	

Validation is an essential requirement for regulatory compliance

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	9	81.8	81.8	81.8
		A	1	9.1	9.1	90.9
		N	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	23	100.0	100.0	100.0

Validation is complex to implement

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	2	18.2	18.2	18.2
		A	2	18.2	18.2	36.4
		N	4	36.4	36.4	72.7
		D	3	27.3	27.3	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	14	60.9	60.9	60.9
		N	6	26.1	26.1	87.0
		D	2	8.7	8.7	95.7
		SD	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

Validation is expensive to implement

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	6	54.5	54.5	63.6
		N	3	27.3	27.3	90.9
		D	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	11	47.8	47.8	47.8
		N	8	34.8	34.8	82.6
		D	3	13.0	13.0	95.7
		SD	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

Facility validation duration - is difficult to estimate

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	7	63.6	63.6	63.6
		N	1	9.1	9.1	72.7
		D	3	27.3	27.3	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	10	43.5	43.5	43.5
		N	3	13.0	13.0	56.5
		D	8	34.8	34.8	91.3
		SD	2	8.7	8.7	100.0
		Total	23	100.0	100.0	

Facility validation duration - adds to overall project duration

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	2	18.2	18.2	18.2
		A	8	72.7	72.7	90.9
		N	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	2	8.7	8.7	8.7
		A	15	65.2	65.2	73.9
		N	1	4.3	4.3	78.3
		D	3	13.0	13.0	91.3
		SD	2	8.7	8.7	100.0
		Total	23	100.0	100.0	

Facility validation cost is - difficult to estimate

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	6	54.5	60.0	60.0
		D	4	36.4	40.0	100.0
		Total	10	90.9	100.0	
	Missing	.00	1	9.1		
	Total		11	100.0		
pharma	Valid	A	9	39.1	40.9	40.9
		N	4	17.4	18.2	59.1
		D	7	30.4	31.8	90.9
		SD	2	8.7	9.1	100.0
		Total	22	95.7	100.0	
	Missing	.00	1	4.3		
	Total		23	100.0		

Facility validation cost is - difficult to control

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	5	45.5	50.0	50.0
		D	5	45.5	50.0	100.0
		Total	10	90.9	100.0	
	Missing	.00	1	9.1		
	Total		11	100.0		
pharma	Valid	A	10	43.5	45.5	45.5
		N	3	13.0	13.6	59.1
		D	9	39.1	40.9	100.0
		Total	22	95.7	100.0	
	Missing	.00	1	4.3		
	Total		23	100.0		

The calculation of facility validation cost is based on - past experience

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	10	90.9	90.9	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	4	17.4	18.2	18.2
		A	14	60.9	63.6	81.8
		N	3	13.0	13.6	95.5
		D	1	4.3	4.5	100.0
		Total	22	95.7	100.0	
	Missing	.00	1	4.3		
	Total		23	100.0		

The calculation of facility validation cost is based on - planning matrix

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	2	18.2	18.2	18.2
		A	8	72.7	72.7	90.9
		D	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	6	26.1	27.3	27.3
		A	12	52.2	54.5	81.8
		N	2	8.7	9.1	90.9
		D	2	8.7	9.1	100.0
		Total	22	95.7	100.0	
	Missing	.00	1	4.3		
	Total		23	100.0		

The calculation of facility validation cost is based on - specialist sub-contractor quotation

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	4	36.4	36.4	45.5
		N	2	18.2	18.2	63.6
		D	2	18.2	18.2	81.8
		SD	2	18.2	18.2	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	1	4.3	4.5	4.5
		A	9	39.1	40.9	45.5
		N	6	26.1	27.3	72.7
		D	6	26.1	27.3	100.0
		Total	22	95.7	100.0	
	Missing	.00	1	4.3		
	Total		23	100.0		

The calculation of facility validation cost is based on - budget percentage sum

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	2	18.2	20.0	20.0
		N	1	9.1	10.0	30.0
		D	5	45.5	50.0	80.0
		SD	2	18.2	20.0	100.0
		Total	10	90.9	100.0	
	Missing	.00	1	9.1		
	Total		11	100.0		
pharma	Valid	SA	1	4.3	4.5	4.5
		A	10	43.5	45.5	50.0
		N	1	4.3	4.5	54.5
		D	9	39.1	40.9	95.5
		SD	1	4.3	4.5	100.0
		Total	22	95.7	100.0	
	Missing	.00	1	4.3		
	Total		23	100.0		

The calculation of facility validation cost is based on - the commissioning time slot at the project end

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	N	2	18.2	18.2	18.2
		D	4	36.4	36.4	54.5
		SD	5	45.5	45.5	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	2	8.7	9.1	9.1
		N	2	8.7	9.1	18.2
		D	9	39.1	40.9	59.1
		SD	9	39.1	40.9	100.0
		Total	22	95.7	100.0	
	Missing	.00	1	4.3		
	Total		23	100.0		

As a percentage of the overall facility Construction, validation costs are - below 5%

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	2	18.2	25.0	25.0
		N	2	18.2	25.0	50.0
		D	2	18.2	25.0	75.0
		SD	2	18.2	25.0	100.0
		Total	8	72.7	100.0	
	Missing	.00	3	27.3		
	Total		11	100.0		
pharma	Valid	SA	1	4.3	6.3	6.3
		A	4	17.4	25.0	31.3
		N	4	17.4	25.0	56.3
		D	2	8.7	12.5	68.8
		SD	5	21.7	31.3	100.0
		Total	16	69.6	100.0	
	Missing	.00	7	30.4		
	Total		23	100.0		

As a percentage of the overall facility Construction, validation costs are - between 5% and 10%

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	12.5	12.5
		A	1	9.1	12.5	25.0
		N	3	27.3	37.5	62.5
		D	3	27.3	37.5	100.0
		Total	8	72.7	100.0	
	Missing	.00	3	27.3		
	Total		11	100.0		
pharma	Valid	SA	1	4.3	6.7	6.7
		A	5	21.7	33.3	40.0
		N	6	26.1	40.0	80.0
		D	3	13.0	20.0	100.0
		Total	15	65.2	100.0	
	Missing	.00	8	34.8		
	Total		23	100.0		

As a percentage of the overall facility Construction, validation costs are - between 10% and 15%

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	14.3	14.3
		A	2	18.2	28.6	42.9
		N	2	18.2	28.6	71.4
		D	1	9.1	14.3	85.7
		SD	1	9.1	14.3	100.0
		Total	7	63.6	100.0	
	Missing	.00	4	36.4		
	Total		11	100.0		
pharma	Valid	SA	2	8.7	12.5	12.5
		A	5	21.7	31.3	43.8
		N	4	17.4	25.0	68.8
		D	4	17.4	25.0	93.8
		SD	1	4.3	6.3	100.0
		Total	16	69.6	100.0	
	Missing	.00	7	30.4		
	Total		23	100.0		

As a percentage of the overall facility Construction, validation costs are - between 15% and 20%

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	N	3	27.3	42.9	42.9
		D	1	9.1	14.3	57.1
		SD	3	27.3	42.9	100.0
		Total	7	63.6	100.0	
	Missing	.00	4	36.4		
	Total		11	100.0		
pharma	Valid	SA	1	4.3	6.3	6.3
		N	4	17.4	25.0	31.3
		D	8	34.8	50.0	81.3
		SD	3	13.0	18.8	100.0
		Total	16	69.6	100.0	
	Missing	.00	7	30.4		
	Total		23	100.0		

As a percentage of the overall facility Construction, validation costs are - above 20%

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	N	2	18.2	28.6	28.6
		D	1	9.1	14.3	42.9
		SD	4	36.4	57.1	100.0
		Total	7	63.6	100.0	
	Missing	.00	4	36.4		
	Total		11	100.0		
pharma	Valid	N	3	13.0	20.0	20.0
		D	4	17.4	26.7	46.7
		SD	8	34.8	53.3	100.0
		Total	15	65.2	100.0	
	Missing	.00	8	34.8		
	Total		23	100.0		

Which areas of a pharmaceutical manufacturing site require validation - site restaurants

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	N	3	27.3	27.3	27.3
		D	3	27.3	27.3	54.5
		SD	5	45.5	45.5	100.0
		Total	11	100.0	100.0	
pharma	Valid	D	3	13.0	13.6	13.6
		SD	19	82.6	86.4	100.0
		Total	22	95.7	100.0	
	Missing	.00	1	4.3		
	Total		23	100.0		

Which areas of a pharmaceutical manufacturing site require validation - product manufacturing ares

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	10	90.9	90.9	90.9
		A	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	22	95.7	95.7	95.7
		A	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

Which areas of a pharmaceutical manufacturing site require validation - product packaging areas

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	8	72.7	72.7	72.7
		A	3	27.3	27.3	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	20	87.0	87.0	87.0
		A	3	13.0	13.0	100.0
		Total	23	100.0	100.0	

Which areas of a pharmaceutical manufacturing site require validation - general circulatory spaces

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	1	9.1	9.1	18.2
		N	7	63.6	63.6	81.8
		D	2	18.2	18.2	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	9	39.1	45.0	45.0
		N	4	17.4	20.0	65.0
		D	4	17.4	20.0	85.0
		SD	3	13.0	15.0	100.0
		Total	20	87.0	100.0	
	Missing	.00	3	13.0		
	Total		23	100.0		

Which areas of a pharmaceutical manufacturing site require validation - dispensaries

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	9	81.8	81.8	81.8
		A	1	9.1	9.1	90.9
		N	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	20	87.0	87.0	87.0
		A	3	13.0	13.0	100.0
		Total	23	100.0	100.0	

Which areas of a pharmaceutical manufacturing site require validation - warehouses

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	2	18.2	18.2	27.3
		N	6	54.5	54.5	81.8
		D	2	18.2	18.2	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	12	52.2	52.2	52.2
		A	11	47.8	47.8	100.0
		Total	23	100.0	100.0	

With reference to Production/packaging product contact areas which of the following require validation - facility internal construction materials

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	3	27.3	27.3	27.3
		A	6	54.5	54.5	81.8
		N	2	18.2	18.2	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	16	69.6	69.6	69.6
		A	5	21.7	21.7	91.3
		N	2	8.7	8.7	100.0
		Total	23	100.0	100.0	

With reference to Production/packaging product contact areas which of the following require validation - HVAC systems

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	7	63.6	63.6	63.6
		A	3	27.3	27.3	90.9
		N	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	20	87.0	87.0	87.0
		A	3	13.0	13.0	100.0
		Total	23	100.0	100.0	

With reference to Production/packaging product contact areas which of the following require validation - room monitoring systems

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	6	54.5	54.5	54.5
		A	4	36.4	36.4	90.9
		N	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	18	78.3	78.3	78.3
		A	5	21.7	21.7	100.0
		Total	23	100.0	100.0	

Which areas of a pharmaceutical manufacturing site require validation - offices

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	N	2	18.2	18.2	18.2
		D	4	36.4	36.4	54.5
		SD	5	45.5	45.5	100.0
		Total	11	100.0	100.0	
pharma	Valid	N	1	4.3	4.5	4.5
		D	2	8.7	9.1	13.6
		SD	19	82.6	86.4	100.0
		Total	22	95.7	100.0	
	Missing	.00	1	4.3		
	Total		23	100.0		

With reference to Production/packaging product contact areas which of the following require validation - purified water systems

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	7	63.6	63.6	63.6
		A	3	27.3	27.3	90.9
		N	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	22	95.7	95.7	95.7
		A	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

With reference to Production/packaging product contact areas which of the following require validation - general indirect utility systems

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	2	18.2	18.2	18.2
		A	3	27.3	27.3	45.5
		N	3	27.3	27.3	72.7
		D	2	18.2	18.2	90.9
		SD	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	1	4.3	4.3	4.3
		A	7	30.4	30.4	34.8
		N	3	13.0	13.0	47.8
		D	6	26.1	26.1	73.9
		SD	6	26.1	26.1	100.0
		Total	23	100.0	100.0	

With reference to Production/packaging product contact areas which of the following require validation - product contact gases

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	7	63.6	63.6	63.6
		A	3	27.3	27.3	90.9
		N	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	21	91.3	91.3	91.3
		A	2	8.7	8.7	100.0
		Total	23	100.0	100.0	

Regulations Governing the validation of pharmaceutical facilities are - too stringent

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	1	9.1	9.1	9.1
		N	3	27.3	27.3	36.4
		D	6	54.5	54.5	90.9
		SD	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	1	4.3	4.5	4.5
		N	4	17.4	18.2	22.7
		D	10	43.5	45.5	68.2
		SD	7	30.4	31.8	100.0
		Total	22	95.7	100.0	
	Missing	.00	1	4.3		
	Total		23	100.0		

Regulations Governing the validation of pharmaceutical facilities are - difficult to understand

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	5	45.5	45.5	45.5
		N	2	18.2	18.2	63.6
		D	3	27.3	27.3	90.9
		SD	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	5	21.7	21.7	21.7
		N	6	26.1	26.1	47.8
		D	7	30.4	30.4	78.3
		SD	5	21.7	21.7	100.0
		Total	23	100.0	100.0	

Regulations Governing the validation of pharmaceutical facilities are - too general and are not detailed enough

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	2	18.2	18.2	27.3
		N	6	54.5	54.5	81.8
		D	1	9.1	9.1	90.9
		SD	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	1	4.3	4.3	4.3
		A	6	26.1	26.1	30.4
		N	7	30.4	30.4	60.9
		D	5	21.7	21.7	82.6
		SD	4	17.4	17.4	100.0
		Total	23	100.0	100.0	

Regulations Governing the validation of pharmaceutical facilities are - vastly different from country to country

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	3	27.3	27.3	36.4
		N	3	27.3	27.3	63.6
		D	3	27.3	27.3	90.9
		SD	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	4	17.4	17.4	17.4
		N	9	39.1	39.1	56.5
		D	9	39.1	39.1	95.7
		SD	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

Regulations Governing the validation of pharmaceutical facilities are - difficult to obtain

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	N	5	45.5	45.5	45.5
		D	4	36.4	36.4	81.8
		SD	2	18.2	18.2	100.0
		Total	11	100.0	100.0	
pharma	Valid	N	6	26.1	26.1	26.1
		D	8	34.8	34.8	60.9
		SD	9	39.1	39.1	100.0
		Total	23	100.0	100.0	

A validated facility is considered compliant when it - fulfils the requirements of the initial design

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	3	27.3	27.3	27.3
		A	3	27.3	27.3	54.5
		N	1	9.1	9.1	63.6
		D	4	36.4	36.4	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	8	34.8	34.8	34.8
		A	11	47.8	47.8	82.6
		D	2	8.7	8.7	91.3
		SD	2	8.7	8.7	100.0
		Total	23	100.0	100.0	

A validated facility is considered compliant when it - is completed on time and at no additional cost

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	N	1	9.1	9.1	9.1
		D	8	72.7	72.7	81.8
		SD	2	18.2	18.2	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	1	4.3	4.3	4.3
		N	2	8.7	8.7	13.0
		D	6	26.1	26.1	39.1
		SD	14	60.9	60.9	100.0
		Total	23	100.0	100.0	

A validated facility is considered compliant when it - satisfies the client

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	1	9.1	9.1	9.1
		N	4	36.4	36.4	45.5
		D	6	54.5	54.5	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	2	8.7	8.7	8.7
		A	8	34.8	34.8	43.5
		D	10	43.5	43.5	87.0
		SD	3	13.0	13.0	100.0
		Total	23	100.0	100.0	

A validated facility is considered compliant when it - satisfies the regulatory inspection

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	9	81.8	81.8	81.8
		A	2	18.2	18.2	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	16	69.6	69.6	69.6
		A	5	21.7	21.7	91.3
		N	1	4.3	4.3	95.7
		D	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

Validation normally starts at the initial design stages of a facility project

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	5	45.5	45.5	54.5
		N	1	9.1	9.1	63.6
		D	4	36.4	36.4	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	13	56.5	56.5	56.5
		A	7	30.4	30.4	87.0
		D	2	8.7	8.7	95.7
		SD	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

Validation normally starts when all construction activities are complete as to allow the installation work to proceed without interuption

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	3	27.3	27.3	27.3
		D	6	54.5	54.5	81.8
		SD	2	18.2	18.2	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	3	13.0	13.0	13.0
		N	1	4.3	4.3	17.4
		D	6	26.1	26.1	43.5
		SD	13	56.5	56.5	100.0
		Total	23	100.0	100.0	

The timing of the implementation is crucial to the success of the whole construction project

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	6	54.5	54.5	54.5
		A	4	36.4	36.4	90.9
		N	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	9	39.1	40.9	40.9
		A	12	52.2	54.5	95.5
		SD	1	4.3	4.5	100.0
		Total	22	95.7	100.0	
	Missing	.00	1	4.3		
	Total		23	100.0		

Project validation should not be necessary if high quality commissioning

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	N	2	18.2	18.2	18.2
		D	7	63.6	63.6	81.8
		SD	2	18.2	18.2	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	2	8.7	8.7	8.7
		N	1	4.3	4.3	13.0
		D	9	39.1	39.1	52.2
		SD	11	47.8	47.8	100.0
		Total	23	100.0	100.0	

A well written commissioning document could be used in lieu of a validation document

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	2	18.2	18.2	18.2
		N	2	18.2	18.2	36.4
		D	6	54.5	54.5	90.9
		SD	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	2	8.7	8.7	8.7
		A	5	21.7	21.7	30.4
		N	3	13.0	13.0	43.5
		D	6	26.1	26.1	69.6
		SD	7	30.4	30.4	100.0
		Total	23	100.0	100.0	

Facility validation should be left to the pharmaceutical client

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	1	9.1	9.1	9.1
		N	3	27.3	27.3	36.4
		D	7	63.6	63.6	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	2	8.7	8.7	8.7
		N	7	30.4	30.4	39.1
		D	10	43.5	43.5	82.6
		SD	4	17.4	17.4	100.0
		Total	23	100.0	100.0	

Validation is generally better left to the organisations who design/install as they have a more detailed understanding of the systems

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	N	3	27.3	27.3	27.3
		D	8	72.7	72.7	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	1	4.3	4.3	4.3
		A	3	13.0	13.0	17.4
		N	6	26.1	26.1	43.5
		D	9	39.1	39.1	82.6
		SD	4	17.4	17.4	100.0
		Total	23	100.0	100.0	

Most construction companies are not sufficiently experienced to complete the validation of a facility i.e. writing protocols, carrying out tests and reporting outcomes

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	6	54.5	54.5	63.6
		D	4	36.4	36.4	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	3	13.0	13.0	13.0
		A	10	43.5	43.5	56.5
		N	3	13.0	13.0	69.6
		D	7	30.4	30.4	100.0
		Total	23	100.0	100.0	

If an installer is testing a system during installation it is wasteful to repeat the tests as part of a validation exercise

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	5	45.5	45.5	45.5
		N	1	9.1	9.1	54.5
		D	5	45.5	45.5	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	1	4.3	4.3	4.3
		A	8	34.8	34.8	39.1
		N	1	4.3	4.3	43.5
		D	10	43.5	43.5	87.0
		SD	3	13.0	13.0	100.0
		Total	23	100.0	100.0	

Commissioning should be used to qualify non-critical systems as it is likely that good engineering practice will ensure a properly installed plant or system

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	9	81.8	81.8	81.8
		D	2	18.2	18.2	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	8	34.8	34.8	34.8
		A	12	52.2	52.2	87.0
		D	3	13.0	13.0	100.0
		Total	23	100.0	100.0	

Projects run more smoothly when an integrated/partnering approach is adopted. i.e all those involved with any aspect of the project have an input into the project, including validation at an early stage

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	5	45.5	45.5	45.5
		A	5	45.5	45.5	90.9
		N	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	15	65.2	65.2	65.2
		A	7	30.4	30.4	95.7
		N	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

Validation is a new area of quality assurance that does not have clear industry guidelines

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	N	3	27.3	27.3	27.3
		D	6	54.5	54.5	81.8
		SD	2	18.2	18.2	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	1	4.3	4.3	4.3
		A	1	4.3	4.3	8.7
		N	3	13.0	13.0	21.7
		D	10	43.5	43.5	65.2
		SD	8	34.8	34.8	100.0
		Total	23	100.0	100.0	

Validation of a facility is worthless unless a system of continued maintenance is in place to ensure that performance levels are within specification

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	3	27.3	27.3	27.3
		A	6	54.5	54.5	81.8
		N	1	9.1	9.1	90.9
		D	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	12	52.2	52.2	52.2
		A	8	34.8	34.8	87.0
		N	1	4.3	4.3	91.3
		D	2	8.7	8.7	100.0
		Total	23	100.0	100.0	

During the facility validation there are usually sufficient systems in place to allow feedback and corrective action if something has been incorrectly designed, installed or commissioned

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	6	54.5	54.5	63.6
		N	3	27.3	27.3	90.9
		D	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	3	13.0	13.6	13.6
		A	9	39.1	40.9	54.5
		N	4	17.4	18.2	72.7
		D	4	17.4	18.2	90.9
		SD	2	8.7	9.1	100.0
		Total	22	95.7	100.0	
	Missing	.00	1	4.3		
	Total		23	100.0		

The PHARMACEUTICAL INDUSTRY is - flexible

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	2	18.2	20.0	20.0
		N	3	27.3	30.0	50.0
		D	4	36.4	40.0	90.0
		SD	1	9.1	10.0	100.0
		Total	10	90.9	100.0	
	Missing	.00	1	9.1		
	Total		11	100.0		
pharma	Valid	A	3	13.0	13.0	13.0
		N	6	26.1	26.1	39.1
		D	11	47.8	47.8	87.0
		SD	3	13.0	13.0	100.0
		Total	23	100.0	100.0	

The PHARMACEUTICAL INDUSTRY is - profit focused

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	7	63.6	63.6	72.7
		N	2	18.2	18.2	90.9
		D	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	5	21.7	21.7	21.7
		A	12	52.2	52.2	73.9
		N	1	4.3	4.3	78.3
		D	5	21.7	21.7	100.0
		Total	23	100.0	100.0	

The PHARMACEUTICAL INDUSTRY is - contractual

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	2	18.2	20.0	20.0
		N	7	63.6	70.0	90.0
		D	1	9.1	10.0	100.0
		Total	10	90.9	100.0	
	Missing	.00	1	9.1		
	Total		11	100.0		
pharma	Valid	SA	2	8.7	8.7	8.7
		A	10	43.5	43.5	52.2
		N	7	30.4	30.4	82.6
		D	4	17.4	17.4	100.0
		Total	23	100.0	100.0	

The PHARMACEUTICAL INDUSTRY is - insular

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	10.0	10.0
		A	2	18.2	20.0	30.0
		N	4	36.4	40.0	70.0
		D	3	27.3	30.0	100.0
		Total	10	90.9	100.0	
	Missing	.00	1	9.1		
	Total		11	100.0		
pharma	Valid	SA	3	13.0	13.0	13.0
		A	10	43.5	43.5	56.5
		N	3	13.0	13.0	69.6
		D	6	26.1	26.1	95.7
		SD	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

The PHARMACEUTICAL INDUSTRY is - efficient

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	4	36.4	36.4	36.4
		N	6	54.5	54.5	90.9
		D	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	2	8.7	8.7	8.7
		N	5	21.7	21.7	30.4
		D	14	60.9	60.9	91.3
		SD	2	8.7	8.7	100.0
		Total	23	100.0	100.0	

The PHARMACEUTICAL INDUSTRY is - research lead

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	6	54.5	54.5	54.5
		N	5	45.5	45.5	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	7	30.4	30.4	30.4
		A	11	47.8	47.8	78.3
		N	4	17.4	17.4	95.7
		D	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

The PHARMACEUTICAL INDUSTRY is - highly regulated

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	3	27.3	27.3	27.3
		A	7	63.6	63.6	90.9
		N	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	16	69.6	72.7	72.7
		A	6	26.1	27.3	100.0
		Total	22	95.7	100.0	
	Missing	.00	1	4.3		
	Total		23	100.0		

The PHARMACEUTICAL INDUSTRY is - adequatley resourced

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	8	72.7	72.7	72.7
		N	3	27.3	27.3	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	5	21.7	21.7	21.7
		A	5	21.7	21.7	43.5
		N	6	26.1	26.1	69.6
		D	6	26.1	26.1	95.7
		SD	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

The PHARMACEUTICAL INDUSTRY is - proactive

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	6	54.5	54.5	54.5
		N	4	36.4	36.4	90.9
		D	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	2	8.7	8.7	8.7
		A	5	21.7	21.7	30.4
		N	14	60.9	60.9	91.3
		D	1	4.3	4.3	95.7
		SD	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

The PHARMACEUTICAL INDUSTRY is - highly technological

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	7	63.6	63.6	72.7
		N	3	27.3	27.3	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	2	8.7	8.7	8.7
		A	10	43.5	43.5	52.2
		N	7	30.4	30.4	82.6
		D	3	13.0	13.0	95.7
		SD	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

Those employed in the PHARMACEUTICAL INDUSTRY - have low job related stress

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	2	18.2	18.2	27.3
		N	7	63.6	63.6	90.9
		D	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	1	4.3	4.3	4.3
		N	2	8.7	8.7	13.0
		D	15	65.2	65.2	78.3
		SD	5	21.7	21.7	100.0
		Total	23	100.0	100.0	

Those employed in the PHARMACEUTICAL INDUSTRY - have high job satisfaction

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	5	45.5	45.5	45.5
		N	6	54.5	54.5	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	1	4.3	4.3	4.3
		A	10	43.5	43.5	47.8
		N	6	26.1	26.1	73.9
		D	5	21.7	21.7	95.7
		SD	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

Those employed in the PHARMACEUTICAL INDUSTRY - receive good pay/employment packages

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	7	63.6	63.6	72.7
		N	3	27.3	27.3	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	2	8.7	8.7	8.7
		A	13	56.5	56.5	65.2
		N	6	26.1	26.1	91.3
		D	2	8.7	8.7	100.0
		Total	23	100.0	100.0	

Those employed in the PHARMACEUTICAL INDUSTRY - are highly motivated

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	4	36.4	36.4	45.5
		N	6	54.5	54.5	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	1	4.3	4.3	4.3
		A	7	30.4	30.4	34.8
		N	11	47.8	47.8	82.6
		D	3	13.0	13.0	95.7
		SD	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

Those employed in the PHARMACEUTICAL INDUSTRY - have a comfortable and safe working environment

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	6	54.5	54.5	63.6
		N	4	36.4	36.4	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	1	4.3	4.3	4.3
		A	14	60.9	60.9	65.2
		N	6	26.1	26.1	91.3
		D	1	4.3	4.3	95.7
		SD	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

Those employed in the PHARMACEUTICAL INDUSTRY - receive adequate job focused training

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	8	72.7	72.7	72.7
		N	3	27.3	27.3	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	3	13.0	13.0	13.0
		A	10	43.5	43.5	56.5
		N	7	30.4	30.4	87.0
		D	2	8.7	8.7	95.7
		SD	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

Those employed in the PHARMACEUTICAL INDUSTRY - generally work in one site/office location and seldom travel for work

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	4	36.4	36.4	45.5
		N	5	45.5	45.5	90.9
		D	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	1	4.3	4.3	4.3
		A	7	30.4	30.4	34.8
		N	6	26.1	26.1	60.9
		D	8	34.8	34.8	95.7
		SD	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

Those employed in the PHARMACEUTICAL INDUSTRY - feel that their job offers sufficient challenges

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	3	27.3	27.3	27.3
		N	8	72.7	72.7	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	2	8.7	8.7	8.7
		A	8	34.8	34.8	43.5
		N	11	47.8	47.8	91.3
		D	1	4.3	4.3	95.7
		SD	1	4.3	4.3	100.0
		Total	23	100.0	100.0	

The CONSTRUCTION INDUSTRY is - flexible

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	10.0	10.0
		A	3	27.3	30.0	40.0
		N	4	36.4	40.0	80.0
		D	2	18.2	20.0	100.0
		Total	10	90.9	100.0	
	Missing	.00	1	9.1		
	Total		11	100.0		
pharma	Valid	A	12	52.2	60.0	60.0
		N	5	21.7	25.0	85.0
		SD	3	13.0	15.0	100.0
		Total	20	87.0	100.0	
	Missing	.00	3	13.0		
	Total		23	100.0		

The CONSTRUCTION INDUSTRY is - profit focused

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	3	27.3	27.3	27.3
		A	6	54.5	54.5	81.8
		N	1	9.1	9.1	90.9
		D	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	11	47.8	52.4	52.4
		A	10	43.5	47.6	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

The CONSTRUCTION INDUSTRY is - contractual

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	4	36.4	36.4	36.4
		A	6	54.5	54.5	90.9
		N	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	11	47.8	52.4	52.4
		A	8	34.8	38.1	90.5
		N	2	8.7	9.5	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

The CONSTRUCTION INDUSTRY is - insular

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	4	36.4	36.4	36.4
		N	5	45.5	45.5	81.8
		D	2	18.2	18.2	100.0
		Total	11	100.0	100.0	
pharma	Valid	SA	1	4.3	4.8	4.8
		A	4	17.4	19.0	23.8
		N	9	39.1	42.9	66.7
		D	7	30.4	33.3	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

The CONSTRUCTION INDUSTRY is - efficient

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	1	9.1	9.1	9.1
		N	6	54.5	54.5	63.6
		D	4	36.4	36.4	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	4	17.4	19.0	19.0
		N	10	43.5	47.6	66.7
		D	6	26.1	28.6	95.2
		SD	1	4.3	4.8	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

The CONSTRUCTION INDUSTRY is - research lead

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	N	3	27.3	27.3	27.3
		D	5	45.5	45.5	72.7
		SD	3	27.3	27.3	100.0
		Total	11	100.0	100.0	
pharma	Valid	N	1	4.3	4.8	4.8
		D	10	43.5	47.6	52.4
		SD	10	43.5	47.6	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

The CONSTRUCTION INDUSTRY is - highly regulated

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	SA	1	9.1	9.1	9.1
		A	3	27.3	27.3	36.4
		N	3	27.3	27.3	63.6
		D	1	9.1	9.1	72.7
		SD	3	27.3	27.3	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	9	39.1	42.9	42.9
		N	8	34.8	38.1	81.0
		D	3	13.0	14.3	95.2
		SD	1	4.3	4.8	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

The CONSTRUCTION INDUSTRY is - adequatley resourced

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	1	9.1	9.1	9.1
		N	4	36.4	36.4	45.5
		D	6	54.5	54.5	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	3	13.0	14.3	14.3
		N	9	39.1	42.9	57.1
		D	7	30.4	33.3	90.5
		SD	2	8.7	9.5	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

The CONSTRUCTION INDUSTRY is - proactive

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	4	36.4	36.4	36.4
		N	6	54.5	54.5	90.9
		D	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	5	21.7	23.8	23.8
		N	8	34.8	38.1	61.9
		D	6	26.1	28.6	90.5
		SD	2	8.7	9.5	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

The CONSTRUCTION INDUSTRY is - highly technological

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	1	9.1	9.1	9.1
		N	7	63.6	63.6	72.7
		D	2	18.2	18.2	90.9
		SD	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	6	26.1	28.6	28.6
		N	7	30.4	33.3	61.9
		D	7	30.4	33.3	95.2
		SD	1	4.3	4.8	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

Those employed in the CONSTRUCTION INDUSTRY - have low job related stress

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	1	9.1	9.1	9.1
		N	2	18.2	18.2	27.3
		D	6	54.5	54.5	81.8
		SD	2	18.2	18.2	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	2	8.7	9.5	9.5
		N	6	26.1	28.6	38.1
		D	9	39.1	42.9	81.0
		SD	4	17.4	19.0	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

Those employed in the CONSTRUCTION INDUSTRY - have high job satisfaction

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	7	63.6	63.6	63.6
		N	3	27.3	27.3	90.9
		D	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	7	30.4	33.3	33.3
		N	12	52.2	57.1	90.5
		D	2	8.7	9.5	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

Those employed in the CONSTRUCTION INDUSTRY - receive good pay/employment packages

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	2	18.2	18.2	18.2
		N	3	27.3	27.3	45.5
		D	5	45.5	45.5	90.9
		SD	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	4	17.4	19.0	19.0
		N	13	56.5	61.9	81.0
		D	4	17.4	19.0	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

Those employed in the CONSTRUCTION INDUSTRY - are highly motivated

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	5	45.5	45.5	45.5
		N	3	27.3	27.3	72.7
		D	3	27.3	27.3	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	4	17.4	19.0	19.0
		N	13	56.5	61.9	81.0
		D	4	17.4	19.0	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

Those employed in the CONSTRUCTION INDUSTRY - have a comfortable and safe working environment

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	N	5	45.5	45.5	45.5
		D	6	54.5	54.5	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	4	17.4	19.0	19.0
		N	6	26.1	28.6	47.6
		D	7	30.4	33.3	81.0
		SD	4	17.4	19.0	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

Those employed in the CONSTRUCTION INDUSTRY - receive adequate job focused training

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	1	9.1	9.1	9.1
		N	6	54.5	54.5	63.6
		D	4	36.4	36.4	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	5	21.7	23.8	23.8
		N	10	43.5	47.6	71.4
		D	5	21.7	23.8	95.2
		SD	1	4.3	4.8	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

Those employed in the CONSTRUCTION INDUSTRY - generally work in one site/office location and seldom travel for work

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	1	9.1	9.1	9.1
		N	1	9.1	9.1	18.2
		D	8	72.7	72.7	90.9
		SD	1	9.1	9.1	100.0
		Total	11	100.0	100.0	
pharma	Valid	N	1	4.3	4.8	4.8
		D	10	43.5	47.6	52.4
		SD	10	43.5	47.6	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

Those employed in the CONSTRUCTION INDUSTRY - feel that their job offers sufficient challenges

Job title			Frequency	Percent	Valid Percent	Cumulative Percent
const	Valid	A	7	63.6	63.6	63.6
		N	1	9.1	9.1	72.7
		D	3	27.3	27.3	100.0
		Total	11	100.0	100.0	
pharma	Valid	A	7	30.4	33.3	33.3
		N	11	47.8	52.4	85.7
		D	3	13.0	14.3	100.0
		Total	21	91.3	100.0	
	Missing	.00	2	8.7		
	Total		23	100.0		

Correlations

Correlations

Job title			Validation normally starts at the initial design stages of a facility project	Years involved in validation
const	Validation normally starts at the initial design stages of a facility project	Pearson Correlation	1	-.106
		Sig. (2-tailed)	.	.756
		N	11	11
	Years involved in validation	Pearson Correlation	-.106	1
		Sig. (2-tailed)	.756	.
		N	11	11
pharma	Validation normally starts at the initial design stages of a facility project	Pearson Correlation	1	-.513*
		Sig. (2-tailed)	.	.012
		N	23	23
	Years involved in validation	Pearson Correlation	-.513*	1
		Sig. (2-tailed)	.012	.
		N	23	23

*. Correlation is significant at the 0.05 level (2-tailed).

Correlations

Job title			Years involved in validation
const	Years involved in validation	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Validation normally starts when all construction activities are complete as to allow the installation work to proceed without interuption	Pearson Correlation	.008
		Sig. (2-tailed)	.981
		N	11
pharma	Years involved in validation	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	Validation normally starts when all construction activities are complete as to allow the installation work to proceed without interuption	Pearson Correlation	.438*
		Sig. (2-tailed)	.037
		N	23

Correlations

Job title			Validation normally starts when all construction activities are complete as to allow the installation work to proceed without interuption
const	Years involved in validation	Pearson Correlation	.008
		Sig. (2-tailed)	.981
		N	11
	Validation normally starts when all construction activities are complete as to allow the installation work to proceed without interuption	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
pharma	Years involved in validation	Pearson Correlation	.438*
		Sig. (2-tailed)	.037
		N	23
	Validation normally starts when all construction activities are complete as to allow the installation work to proceed without interuption	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23

*. Correlation is significant at the 0.05 level (2-tailed).

Correlations

Correlations

Job title			Years involved in validation
const	Years involved in validation	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	As a percentage of the overall facility Construction, validation costs are - below 5%	Pearson Correlation	.893**
		Sig. (2-tailed)	.003
		N	8
pharma	Years involved in validation	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	As a percentage of the overall facility Construction, validation costs are - below 5%	Pearson Correlation	.081
		Sig. (2-tailed)	.766
		N	16

Correlations

Job title			As a percentage of the overall facility Construction, validation costs are - below 5%
const	Years involved in validation	Pearson Correlation	.893**
		Sig. (2-tailed)	.003
		N	8
	As a percentage of the overall facility Construction, validation costs are - below 5%	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	8
pharma	Years involved in validation	Pearson Correlation	.081
		Sig. (2-tailed)	.766
		N	16
	As a percentage of the overall facility Construction, validation costs are - below 5%	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	16

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

Correlations

Job title			Years involved in validation
const	Years involved in validation	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	As a percentage of the overall facility Construction, validation costs are - between 5% and 10%	Pearson Correlation	-.289
		Sig. (2-tailed)	.488
		N	8
pharma	Years involved in validation	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	As a percentage of the overall facility Construction, validation costs are - between 5% and 10%	Pearson Correlation	.173
		Sig. (2-tailed)	.537
		N	15

Correlations

Job title			As a percentage of the overall facility Construction, validation costs are - between 5% and 10%
const	Years involved in validation	Pearson Correlation	-.289
		Sig. (2-tailed)	.488
		N	8
	As a percentage of the overall facility Construction, validation costs are - between 5% and 10%	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	8
pharma	Years involved in validation	Pearson Correlation	.173
		Sig. (2-tailed)	.537
		N	15
	As a percentage of the overall facility Construction, validation costs are - between 5% and 10%	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	15

Correlations

Correlations

Job title			Years involved in validation
const	Years involved in validation	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	As a percentage of the overall facility Construction, validation costs are - between 10% and 15%	Pearson Correlation	-.846*
		Sig. (2-tailed)	.016
		N	7
pharma	Years involved in validation	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	As a percentage of the overall facility Construction, validation costs are - between 10% and 15%	Pearson Correlation	.322
		Sig. (2-tailed)	.225
		N	16

Correlations

Job title			As a percentage of the overall facility Construction, validation costs are - between 10% and 15%
const	Years involved in validation	Pearson Correlation	-.846*
		Sig. (2-tailed)	.016
		N	7
	As a percentage of the overall facility Construction, validation costs are - between 10% and 15%	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	7
pharma	Years involved in validation	Pearson Correlation	.322
		Sig. (2-tailed)	.225
		N	16
	As a percentage of the overall facility Construction, validation costs are - between 10% and 15%	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	16

*. Correlation is significant at the 0.05 level (2-tailed).

Correlations

Correlations

Job title			Years involved in validation
const	Years involved in validation	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	As a percentage of the overall facility Construction, validation costs are - between 15% and 20%	Pearson Correlation	-.370
		Sig. (2-tailed)	.413
		N	7
pharma	Years involved in validation	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	As a percentage of the overall facility Construction, validation costs are - between 15% and 20%	Pearson Correlation	.442
		Sig. (2-tailed)	.087
		N	16

Correlations

Job title			As a percentage of the overall facility Construction, validation costs are - between 15% and 20%
const	Years involved in validation	Pearson Correlation	-.370
		Sig. (2-tailed)	.413
		N	7
	As a percentage of the overall facility Construction, validation costs are - between 15% and 20%	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	7
pharma	Years involved in validation	Pearson Correlation	.442
		Sig. (2-tailed)	.087
		N	16
	As a percentage of the overall facility Construction, validation costs are - between 15% and 20%	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	16

Correlations

Correlations

Job title			Years involved in validation
const	Years involved in validation	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	As a percentage of the overall facility Construction, validation costs are - above 20%	Pearson Correlation	.056
		Sig. (2-tailed)	.906
		N	7
pharma	Years involved in validation	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	As a percentage of the overall facility Construction, validation costs are - above 20%	Pearson Correlation	.624*
		Sig. (2-tailed)	.013
		N	15

Correlations

Job title			As a percentage of the overall facility Construction, validation costs are - above 20%
const	Years involved in validation	Pearson Correlation	.056
		Sig. (2-tailed)	.906
		N	7
	As a percentage of the overall facility Construction, validation costs are - above 20%	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	7
pharma	Years involved in validation	Pearson Correlation	.624*
		Sig. (2-tailed)	.013
		N	15
	As a percentage of the overall facility Construction, validation costs are - above 20%	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	15

*. Correlation is significant at the 0.05 level (2-tailed).

Correlations

Correlations

Job title			Years involved in validation
const	Years involved in validation	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - difficult to obtain	Pearson Correlation	.481
		Sig. (2-tailed)	.134
		N	11
pharma	Years involved in validation	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	Regulations Governing the validation of pharmaceutical facilities are - difficult to obtain	Pearson Correlation	.258
		Sig. (2-tailed)	.234
		N	23

Correlations

Job title			Regulations Governing the validation of pharmaceutical facilities are - difficult to obtain
const	Years involved in validation	Pearson Correlation	.481
		Sig. (2-tailed)	.134
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - difficult to obtain	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
pharma	Years involved in validation	Pearson Correlation	.258
		Sig. (2-tailed)	.234
		N	23
	Regulations Governing the validation of pharmaceutical facilities are - difficult to obtain	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23

Correlations

Job title			Regulations Governing the validation of pharmaceutical facilities are - vastly different from country to country
const	Years involved in validation	Pearson Correlation	.754**
		Sig. (2-tailed)	.007
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - vastly different from country to country	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
pharma	Years involved in validation	Pearson Correlation	.185
		Sig. (2-tailed)	.398
		N	23
	Regulations Governing the validation of pharmaceutical facilities are - vastly different from country to country	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

Correlations

Job title			Years involved in validation	A validated facility is considered compliant when it - is completed on time and at no additional cost
const	Years involved in validation	Pearson Correlation	1	.685*
		Sig. (2-tailed)	.	.020
		N	11	11
	A validated facility is considered compliant when it - is completed on time and at no additional cost	Pearson Correlation	.685*	1
		Sig. (2-tailed)	.020	.
		N	11	11
pharma	Years involved in validation	Pearson Correlation	1	-.245
		Sig. (2-tailed)	.	.259
		N	23	23
	A validated facility is considered compliant when it - is completed on time and at no additional cost	Pearson Correlation	-.245	1
		Sig. (2-tailed)	.259	.
		N	23	23

*. Correlation is significant at the 0.05 level (2-tailed).

Correlations

Correlations

Job title			Years involved in validation	A well written commissioning document could be used in lieu of a validation document
const	Years involved in validation	Pearson Correlation	1	-.068
		Sig. (2-tailed)	.	.844
		N	11	11
	A well written commissioning document could be used in lieu of a validation document	Pearson Correlation	-.068	1
		Sig. (2-tailed)	.844	.
		N	11	11
pharma	Years involved in validation	Pearson Correlation	1	-.434*
		Sig. (2-tailed)	.	.039
		N	23	23
	A well written commissioning document could be used in lieu of a validation document	Pearson Correlation	-.434*	1
		Sig. (2-tailed)	.039	.
		N	23	23

*. Correlation is significant at the 0.05 level (2-tailed).

Correlations

Correlations

Job title			Vaidate if asked for by client	Validation is complex to implement
const	Vaidate if asked for by client	Pearson Correlation	1	.772**
		Sig. (2-tailed)	.	.009
		N	10	10
	Validation is complex to implement	Pearson Correlation	.772**	1
		Sig. (2-tailed)	.009	.
		N	10	11
pharma	Vaidate if asked for by client	Pearson Correlation	1	-.052
		Sig. (2-tailed)	.	.813
		N	23	23
	Validation is complex to implement	Pearson Correlation	-.052	1
		Sig. (2-tailed)	.813	.
		N	23	23

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

Correlations

Job title			Validation is complex to implement
const	Validation is complex to implement	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Validation is expensive to implement	Pearson Correlation	.682*
		Sig. (2-tailed)	.021
		N	11
pharma	Validation is complex to implement	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	Validation is expensive to implement	Pearson Correlation	.461*
		Sig. (2-tailed)	.027
		N	23

Correlations

Job title			Validation is expensive to implement
const	Validation is complex to implement	Pearson Correlation	.682*
		Sig. (2-tailed)	.021
		N	11
	Validation is expensive to implement	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
pharma	Validation is complex to implement	Pearson Correlation	.461*
		Sig. (2-tailed)	.027
		N	23
	Validation is expensive to implement	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23

*. Correlation is significant at the 0.05 level (2-tailed).

Correlations

Correlations

Job title			Validation is complex to implement
const	Validation is complex to implement	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Facility validation cost is - difficult to estimate	Pearson Correlation	.303
		Sig. (2-tailed)	.395
		N	10
pharma	Validation is complex to implement	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	Facility validation cost is - difficult to estimate	Pearson Correlation	.462*
		Sig. (2-tailed)	.031
		N	22

Correlations

Job title			Facility validation cost is - difficult to estimate
const	Validation is complex to implement	Pearson Correlation	.303
		Sig. (2-tailed)	.395
		N	10
	Facility validation cost is - difficult to estimate	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	10
pharma	Validation is complex to implement	Pearson Correlation	.462*
		Sig. (2-tailed)	.031
		N	22
	Facility validation cost is - difficult to estimate	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	22

*. Correlation is significant at the 0.05 level (2-tailed).

Correlations

Correlations

Job title			Validation is complex to implement
const	Validation is complex to implement	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Facility validation duration - is difficult to estimate	Pearson Correlation	.187
		Sig. (2-tailed)	.582
		N	11
pharma	Validation is complex to implement	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	Facility validation duration - is difficult to estimate	Pearson Correlation	.491*
		Sig. (2-tailed)	.017
		N	23

Correlations

Job title			Facility validation duration - is difficult to estimate
const	Validation is complex to implement	Pearson Correlation	.187
		Sig. (2-tailed)	.582
		N	11
	Facility validation duration - is difficult to estimate	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
pharma	Validation is complex to implement	Pearson Correlation	.491*
		Sig. (2-tailed)	.017
		N	23
	Facility validation duration - is difficult to estimate	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23

*. Correlation is significant at the 0.05 level (2-tailed).

Correlations

Correlations

Job title			Id
const	Id	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Facility validation duration - is difficult to estimate	Pearson Correlation	-.301
		Sig. (2-tailed)	.368
		N	11
pharma	Id	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	Facility validation duration - is difficult to estimate	Pearson Correlation	-.505*
		Sig. (2-tailed)	.014
		N	23

Correlations

Job title			Facility validation duration - is difficult to estimate
const	Id	Pearson Correlation	-.301
		Sig. (2-tailed)	.368
		N	11
	Facility validation duration - is difficult to estimate	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
pharma	Id	Pearson Correlation	-.505*
		Sig. (2-tailed)	.014
		N	23
	Facility validation duration - is difficult to estimate	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23

*. Correlation is significant at the 0.05 level (2-tailed).

Correlations

Correlations

Job title			Facility validation duration - is difficult to estimate
const	Facility validation duration - is difficult to estimate	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Facility validation cost is - difficult to estimate	Pearson Correlation	.499
		Sig. (2-tailed)	.142
		N	10
pharma	Facility validation duration - is difficult to estimate	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	Facility validation cost is - difficult to estimate	Pearson Correlation	.776**
		Sig. (2-tailed)	.000
		N	22

Correlations

Job title			Facility validation cost is - difficult to estimate
const	Facility validation duration - is difficult to estimate	Pearson Correlation	.499
		Sig. (2-tailed)	.142
		N	10
	Facility validation cost is - difficult to estimate	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	10
pharma	Facility validation duration - is difficult to estimate	Pearson Correlation	.776**
		Sig. (2-tailed)	.000
		N	22
	Facility validation cost is - difficult to estimate	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	22

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

Correlations

Job title			Regulations Governing the validation of pharmaceutical facilities are - difficult to understand
const	Regulations Governing the validation of pharmaceutical facilities are - difficult to understand	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - too general and are not detailed enough	Pearson Correlation	.787**
		Sig. (2-tailed)	.004
		N	11
pharma	Regulations Governing the validation of pharmaceutical facilities are - difficult to understand	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	Regulations Governing the validation of pharmaceutical facilities are - too general and are not detailed enough	Pearson Correlation	.771**
		Sig. (2-tailed)	.000
		N	23

Correlations

Job title			Regulations Governing the validation of pharmaceutical facilities are - too general and are not detailed enough
const	Regulations Governing the validation of pharmaceutical facilities are - difficult to understand	Pearson Correlation	.787**
		Sig. (2-tailed)	.004
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - too general and are not detailed enough	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
pharma	Regulations Governing the validation of pharmaceutical facilities are - difficult to understand	Pearson Correlation	.771**
		Sig. (2-tailed)	.000
		N	23
	Regulations Governing the validation of pharmaceutical facilities are - too general and are not detailed enough	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

Correlations

Job title			Which areas of a pharmaceutical manufacturing site require validation - product manufacturing ares
const	Which areas of a pharmaceutical manufacturing site require validation - product manufacturing ares	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - product packaging areas	Pearson Correlation	.516
		Sig. (2-tailed)	.104
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - dispensaries	Pearson Correlation	.373
		Sig. (2-tailed)	.259
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - warehouses	Pearson Correlation	-.311
		Sig. (2-tailed)	.353
		N	11
pharma	Which areas of a pharmaceutical manufacturing site require validation - product manufacturing ares	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - product packaging areas	Pearson Correlation	.550**
		Sig. (2-tailed)	.006
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - dispensaries	Pearson Correlation	.550**
		Sig. (2-tailed)	.006
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - warehouses	Pearson Correlation	.223
		Sig. (2-tailed)	.307
		N	23

Correlations

Job title			Which areas of a pharmaceutical manufacturing site require validation - product packaging areas
const	Which areas of a pharmaceutical manufacturing site require validation - product manufacturing ares	Pearson Correlation	.516
		Sig. (2-tailed)	.104
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - product packaging areas	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - dispensaries	Pearson Correlation	.060
		Sig. (2-tailed)	.860
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - warehouses	Pearson Correlation	-.111
		Sig. (2-tailed)	.744
		N	11
pharma	Which areas of a pharmaceutical manufacturing site require validation - product manufacturing ares	Pearson Correlation	.550**
		Sig. (2-tailed)	.006
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - product packaging areas	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - dispensaries	Pearson Correlation	.617**
		Sig. (2-tailed)	.002
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - warehouses	Pearson Correlation	.405
		Sig. (2-tailed)	.056
		N	23

Correlations

Job title			Which areas of a pharmaceutical manufacturing site require validation - dispensaries
const	Which areas of a pharmaceutical manufacturing site require validation - product manufacturing ares	Pearson Correlation	.373
		Sig. (2-tailed)	.259
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - product packaging areas	Pearson Correlation	.060
		Sig. (2-tailed)	.860
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - dispensaries	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - warehouse	Pearson Correlation	-.080
		Sig. (2-tailed)	.814
		N	11
pharma	Which areas of a pharmaceutical manufacturing site require validation - product manufacturing ares	Pearson Correlation	.550**
		Sig. (2-tailed)	.006
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - product packaging areas	Pearson Correlation	.617**
		Sig. (2-tailed)	.002
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - dispensaries	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - warehouse	Pearson Correlation	.405
		Sig. (2-tailed)	.056
		N	23

Correlations

Job title			Which areas of a pharmaceutical manufacturing site require validation - warehouses
const	Which areas of a pharmaceutical manufacturing site require validation - product manufacturing ares	Pearson Correlation	-.311
		Sig. (2-tailed)	.353
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - product packaging areas	Pearson Correlation	-.111
		Sig. (2-tailed)	.744
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - dispensaries	Pearson Correlation	-.080
		Sig. (2-tailed)	.814
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - warehouses	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
pharma	Which areas of a pharmaceutical manufacturing site require validation - product manufacturing ares	Pearson Correlation	.223
		Sig. (2-tailed)	.307
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - product packaging areas	Pearson Correlation	.405
		Sig. (2-tailed)	.056
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - dispensaries	Pearson Correlation	.405
		Sig. (2-tailed)	.056
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - warehouses	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

Correlations

Job title			Regulations Governing the validation of pharmaceutical facilities are - too stringent
const	Regulations Governing the validation of pharmaceutical facilities are - too stringent	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - difficult to understand	Pearson Correlation	.677*
		Sig. (2-tailed)	.022
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - too general and are not detailed enough	Pearson Correlation	.430
		Sig. (2-tailed)	.186
		N	11
	Regulations Governing the validation of pharmaceutical facilities [illegible]	Pearson Correlation	.731*
		Sig. (2-tailed)	.011
		N	11
	Regulations Governing the validation of pharmaceutical facilities [illegible]	Pearson Correlation	.457
		Sig. (2-tailed)	.157
		N	11
pharma	Regulations Governing the validation of pharmaceutical facilities are - too stringent	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	22
	Regulations Governing the validation of pharmaceutical facilities are - difficult to understand	Pearson Correlation	.075
		Sig. (2-tailed)	.739
		N	22
	Regulations Governing the validation of pharmaceutical facilities are - too general and are not detailed enough	Pearson Correlation	.035
		Sig. (2-tailed)	.876
		N	22
	Regulations Governing the validation of pharmaceutical facilities [illegible]	Pearson Correlation	-.156
		Sig. (2-tailed)	.488
		N	22
	Regulations Governing the validation of pharmaceutical facilities [illegible]	Pearson Correlation	.271
		Sig. (2-tailed)	.222
		N	22

Correlations

Job title			Regulations Governing the validation of pharmaceutical facilities are - difficult to understand
const	Regulations Governing the validation of pharmaceutical facilities are - too stringent	Pearson Correlation	.677*
		Sig. (2-tailed)	.022
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - difficult to understand	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - too general and are not detailed enough	Pearson Correlation	.787**
		Sig. (2-tailed)	.004
		N	11
	Regulations Governing the validation of pharmaceutical facilities [illegible]	Pearson Correlation	.694*
		Sig. (2-tailed)	.018
		N	11
	Regulations Governing the validation of pharmaceutical facilities [illegible]	Pearson Correlation	.581
		Sig. (2-tailed)	.061
		N	11
pharma	Regulations Governing the validation of pharmaceutical facilities are - too stringent	Pearson Correlation	.075
		Sig. (2-tailed)	.739
		N	22
	Regulations Governing the validation of pharmaceutical facilities are - difficult to understand	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	Regulations Governing the validation of pharmaceutical facilities are - too general and are not detailed enough	Pearson Correlation	.771**
		Sig. (2-tailed)	.000
		N	23
	Regulations Governing the validation of pharmaceutical facilities [illegible]	Pearson Correlation	.427*
		Sig. (2-tailed)	.042
		N	23
	Regulations Governing the validation of pharmaceutical facilities [illegible]	Pearson Correlation	.693**
		Sig. (2-tailed)	.000
		N	23

Correlations

Job title			Regulations Governing the validation of pharmaceutical facilities are - too general and are not detailed enough
const	Regulations Governing the validation of pharmaceutical facilities are - too stringent	Pearson Correlation	.430
		Sig. (2-tailed)	.186
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - difficult to understand	Pearson Correlation	.787**
		Sig. (2-tailed)	.004
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - too general and are not detailed enough	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - vastly different from	Pearson Correlation	.405
		Sig. (2-tailed)	.217
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - difficult to obtain	Pearson Correlation	.454
		Sig. (2-tailed)	.161
		N	11
pharma	Regulations Governing the validation of pharmaceutical facilities are - too stringent	Pearson Correlation	.035
		Sig. (2-tailed)	.876
		N	22
	Regulations Governing the validation of pharmaceutical facilities are - difficult to understand	Pearson Correlation	.771**
		Sig. (2-tailed)	.000
		N	23
	Regulations Governing the validation of pharmaceutical facilities are - too general and are not detailed enough	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	Regulations Governing the validation of pharmaceutical facilities are - vastly different from	Pearson Correlation	.260
		Sig. (2-tailed)	.231
		N	23
	Regulations Governing the validation of pharmaceutical facilities are - difficult to obtain	Pearson Correlation	.351
		Sig. (2-tailed)	.100
		N	23

Correlations

Job title			Regulations Governing the validation of pharmaceutical facilities are - vastly different from country to country
const	Regulations Governing the validation of pharmaceutical facilities are - too stringent	Pearson Correlation	.731*
		Sig. (2-tailed)	.011
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - difficult to understand	Pearson Correlation	.694*
		Sig. (2-tailed)	.018
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - too general and are not detailed enough	Pearson Correlation	.405
		Sig. (2-tailed)	.217
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - vastly different from country to country	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - difficult to obtain	Pearson Correlation	.752**
		Sig. (2-tailed)	.008
		N	11
pharma	Regulations Governing the validation of pharmaceutical facilities are - too stringent	Pearson Correlation	-.156
		Sig. (2-tailed)	.488
		N	22
	Regulations Governing the validation of pharmaceutical facilities are - difficult to understand	Pearson Correlation	.427*
		Sig. (2-tailed)	.042
		N	23
	Regulations Governing the validation of pharmaceutical facilities are - too general and are not detailed enough	Pearson Correlation	.260
		Sig. (2-tailed)	.231
		N	23
	Regulations Governing the validation of pharmaceutical facilities are - vastly different from country to country	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	Regulations Governing the validation of pharmaceutical facilities are - difficult to obtain	Pearson Correlation	.413
		Sig. (2-tailed)	.050
		N	23

Correlations

Job title			Regulations Governing the validation of pharmaceutical facilities are - difficult to obtain
const	Regulations Governing the validation of pharmaceutical facilities are - too stringent	Pearson Correlation	.457
		Sig. (2-tailed)	.157
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - difficult to understand	Pearson Correlation	.581
		Sig. (2-tailed)	.061
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - too general and are not detailed enough	Pearson Correlation	.454
		Sig. (2-tailed)	.161
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - vastly different from	Pearson Correlation	.752**
		Sig. (2-tailed)	.008
		N	11
	Regulations Governing the validation of pharmaceutical facilities are - difficult to obtain	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
pharma	Regulations Governing the validation of pharmaceutical facilities are - too stringent	Pearson Correlation	.271
		Sig. (2-tailed)	.222
		N	22
	Regulations Governing the validation of pharmaceutical facilities are - difficult to understand	Pearson Correlation	.693**
		Sig. (2-tailed)	.000
		N	23
	Regulations Governing the validation of pharmaceutical facilities are - too general and are not detailed enough	Pearson Correlation	.351
		Sig. (2-tailed)	.100
		N	23
	Regulations Governing the validation of pharmaceutical facilities are - vastly different from	Pearson Correlation	.413
		Sig. (2-tailed)	.050
		N	23
	Regulations Governing the validation of pharmaceutical facilities are - difficult to obtain	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

Correlations

Job title			Id
const	Id	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - offices	Pearson Correlation	.006
		Sig. (2-tailed)	.986
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - site restaurants	Pearson Correlation	.014
		Sig. (2-tailed)	.968
		N	11
pharma	Id	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - offices	Pearson Correlation	-.341
		Sig. (2-tailed)	.120
		N	22
	Which areas of a pharmaceutical manufacturing site require validation - site restaurants	Pearson Correlation	-.330
		Sig. (2-tailed)	.134
		N	22

Correlations

Job title			Which areas of a pharmaceutical manufacturing site require validation - offices
const	Id	Pearson Correlation	.006
		Sig. (2-tailed)	.986
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - offices	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - site restaurants	Pearson Correlation	.939**
		Sig. (2-tailed)	.000
		N	11
pharma	Id	Pearson Correlation	-.341
		Sig. (2-tailed)	.120
		N	22
	Which areas of a pharmaceutical manufacturing site require validation - offices	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	22
	Which areas of a pharmaceutical manufacturing site require validation - site restaurants	Pearson Correlation	.935**
		Sig. (2-tailed)	.000
		N	22

Correlations

Job title			Which areas of a pharmaceutical manufacturing site require validation - site restaurants
const	Id	Pearson Correlation	.014
		Sig. (2-tailed)	.968
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - offices	Pearson Correlation	.939**
		Sig. (2-tailed)	.000
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - site restaurants	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
pharma	Id	Pearson Correlation	-.330
		Sig. (2-tailed)	.134
		N	22
	Which areas of a pharmaceutical manufacturing site require validation - offices	Pearson Correlation	.935**
		Sig. (2-tailed)	.000
		N	22
	Which areas of a pharmaceutical manufacturing site require validation - site restaurants	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	22

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

Correlations

Job title			Id
const	Id	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - product manufacturing ares	Pearson Correlation	-.157
		Sig. (2-tailed)	.644
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - product packaging areas	Pearson Correlation	.096
		Sig. (2-tailed)	.778
		N	11
pharma	Id	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - product manufacturing ares	Pearson Correlation	-.462*
		Sig. (2-tailed)	.027
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - product packaging areas	Pearson Correlation	-.388
		Sig. (2-tailed)	.068
		N	23

Correlations

Job title			Which areas of a pharmaceutical manufacturing site require validation - product manufacturing ares
const	Id	Pearson Correlation	-.157
		Sig. (2-tailed)	.644
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - product manufacturing ares	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - product packaging areas	Pearson Correlation	.516
		Sig. (2-tailed)	.104
		N	11
pharma	Id	Pearson Correlation	-.462*
		Sig. (2-tailed)	.027
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - product manufacturing ares	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - product packaging areas	Pearson Correlation	.550**
		Sig. (2-tailed)	.006
		N	23

Correlations

Job title			Which areas of a pharmaceutical manufacturing site require validation - product packaging areas
const	Id	Pearson Correlation	.096
		Sig. (2-tailed)	.778
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - product manufacturing ares	Pearson Correlation	.516
		Sig. (2-tailed)	.104
		N	11
	Which areas of a pharmaceutical manufacturing site require validation - product packaging areas	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
pharma	Id	Pearson Correlation	-.388
		Sig. (2-tailed)	.068
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - product manufacturing ares	Pearson Correlation	.550**
		Sig. (2-tailed)	.006
		N	23
	Which areas of a pharmaceutical manufacturing site require validation - product packaging areas	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

Correlations

Job title			Id	The CONSTRUCTION INDUSTRY is - highly regulated
const	Id	Pearson Correlation	1	.181
		Sig. (2-tailed)	.	.595
		N	11	11
	The CONSTRUCTION INDUSTRY is - highly regulated	Pearson Correlation	.181	1
		Sig. (2-tailed)	.595	.
		N	11	11
pharma	Id	Pearson Correlation	1	-.520*
		Sig. (2-tailed)	.	.016
		N	23	21
	The CONSTRUCTION INDUSTRY is - highly regulated	Pearson Correlation	-.520*	1
		Sig. (2-tailed)	.016	.
		N	21	21

*. Correlation is significant at the 0.05 level (2-tailed).

Correlations

Correlations

Job title			Id
const	Id	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	The PHARMACEUTICAL INDUSTRY is - highly technological	Pearson Correlation	.420
		Sig. (2-tailed)	.199
		N	11
	The PHARMACEUTICAL INDUSTRY is - research lead	Pearson Correlation	.058
		Sig. (2-tailed)	.865
		N	11
pharma	Id	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	The PHARMACEUTICAL INDUSTRY is - highly technological	Pearson Correlation	.061
		Sig. (2-tailed)	.782
		N	23
	The PHARMACEUTICAL INDUSTRY is - research lead	Pearson Correlation	-.013
		Sig. (2-tailed)	.954
		N	23

Correlations

Job title			The PHARMACEUTICAL INDUSTRY is - highly technological
const	Id	Pearson Correlation	.420
		Sig. (2-tailed)	.199
		N	11
	The PHARMACEUTICAL INDUSTRY is - highly technological	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	The PHARMACEUTICAL INDUSTRY is - research lead	Pearson Correlation	.664*
		Sig. (2-tailed)	.026
		N	11
pharma	Id	Pearson Correlation	.061
		Sig. (2-tailed)	.782
		N	23
	The PHARMACEUTICAL INDUSTRY is - highly technological	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	The PHARMACEUTICAL INDUSTRY is - research lead	Pearson Correlation	.536**
		Sig. (2-tailed)	.008
		N	23

Correlations

Job title			The PHARMACEUTICAL INDUSTRY is - research lead
const	Id	Pearson Correlation	.058
		Sig. (2-tailed)	.865
		N	11
	The PHARMACEUTICAL INDUSTRY is - highly technological	Pearson Correlation	.664*
		Sig. (2-tailed)	.026
		N	11
	The PHARMACEUTICAL INDUSTRY is - research lead	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
pharma	Id	Pearson Correlation	-.013
		Sig. (2-tailed)	.954
		N	23
	The PHARMACEUTICAL INDUSTRY is - highly technological	Pearson Correlation	.536**
		Sig. (2-tailed)	.008
		N	23
	The PHARMACEUTICAL INDUSTRY is - research lead	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

Correlations

Job title			Id
const	Id	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	The PHARMACEUTICAL INDUSTRY is - highly technological	Pearson Correlation	.420
		Sig. (2-tailed)	.199
		N	11
	The PHARMACEUTICAL INDUSTRY is - efficient	Pearson Correlation	.427
		Sig. (2-tailed)	.190
		N	11
pharma	Id	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	The PHARMACEUTICAL INDUSTRY is - highly technological	Pearson Correlation	.061
		Sig. (2-tailed)	.782
		N	23
	The PHARMACEUTICAL INDUSTRY is - efficient	Pearson Correlation	.151
		Sig. (2-tailed)	.492
		N	23

Correlations

Job title			The PHARMACEUTICAL INDUSTRY is - highly technological
const	Id	Pearson Correlation	.420
		Sig. (2-tailed)	.199
		N	11
	The PHARMACEUTICAL INDUSTRY is - highly technological	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
	The PHARMACEUTICAL INDUSTRY is - efficient	Pearson Correlation	.140
		Sig. (2-tailed)	.682
		N	11
pharma	Id	Pearson Correlation	.061
		Sig. (2-tailed)	.782
		N	23
	The PHARMACEUTICAL INDUSTRY is - highly technological	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23
	The PHARMACEUTICAL INDUSTRY is - efficient	Pearson Correlation	.497*
		Sig. (2-tailed)	.016
		N	23

Correlations

Job title			The PHARMACEUTICAL INDUSTRY is - efficient
const	Id	Pearson Correlation	.427
		Sig. (2-tailed)	.190
		N	11
	The PHARMACEUTICAL INDUSTRY is - highly technological	Pearson Correlation	.140
		Sig. (2-tailed)	.682
		N	11
	The PHARMACEUTICAL INDUSTRY is - efficient	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
pharma	Id	Pearson Correlation	.151
		Sig. (2-tailed)	.492
		N	23
	The PHARMACEUTICAL INDUSTRY is - highly technological	Pearson Correlation	.497*
		Sig. (2-tailed)	.016
		N	23
	The PHARMACEUTICAL INDUSTRY is - efficient	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	23

*. Correlation is significant at the 0.05 level (2-tailed).

Correlations

Correlations

Job title			Id	Those employed in the CONSTRUCTION INDUSTRY - receive good pay/employment packages
const	Id	Pearson Correlation	1	-.741**
		Sig. (2-tailed)	.	.009
		N	11	11
	Those employed in the CONSTRUCTION INDUSTRY - receive good pay/employment packages	Pearson Correlation	-.741**	1
		Sig. (2-tailed)	.009	.
		N	11	11
pharma	Id	Pearson Correlation	1	.121
		Sig. (2-tailed)	.	.600
		N	23	21
	Those employed in the CONSTRUCTION INDUSTRY - receive good pay/employment packages	Pearson Correlation	.121	1
		Sig. (2-tailed)	.600	.
		N	21	21

**. Correlation is significant at the 0.01 level (2-tailed).

Correlations

Correlations

Job title			Id	Those employed in the PHARMACEUTICAL INDUSTRY - receive adequate job focused training
const	Id	Pearson Correlation	1	.240
		Sig. (2-tailed)	.	.478
		N	11	11
	Those employed in the PHARMACEUTICAL INDUSTRY - receive adequate job focused training	Pearson Correlation	.240	1
		Sig. (2-tailed)	.478	.
		N	11	11
	Those employed in the CONSTRUCTION INDUSTRY - receive adequate job focused training	Pearson Correlation	-.199	.060
		Sig. (2-tailed)	.557	.860
		N	11	11
pharma	Id	Pearson Correlation	1	.278
		Sig. (2-tailed)	.	.199
		N	23	23
	Those employed in the PHARMACEUTICAL INDUSTRY - receive adequate job focused training	Pearson Correlation	.278	1
		Sig. (2-tailed)	.199	.
		N	23	23
	Those employed in the CONSTRUCTION INDUSTRY - receive adequate job focused training	Pearson Correlation	-.518*	-.132
		Sig. (2-tailed)	.016	.569
		N	21	21

Correlations

Job title			Those employed in the CONSTRUCTION INDUSTRY - receive adequate job focused training
const	Id	Pearson Correlation	-.199
		Sig. (2-tailed)	.557
		N	11
	Those employed in the PHARMACEUTICAL INDUSTRY - receive adequate job focused training	Pearson Correlation	.060
		Sig. (2-tailed)	.860
		N	11
	Those employed in the CONSTRUCTION INDUSTRY - receive adequate job focused training	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	11
pharma	Id	Pearson Correlation	-.518*
		Sig. (2-tailed)	.016
		N	21
	Those employed in the PHARMACEUTICAL INDUSTRY - receive adequate job focused training	Pearson Correlation	-.132
		Sig. (2-tailed)	.569
		N	21
	Those employed in the CONSTRUCTION INDUSTRY - receive adequate job focused training	Pearson Correlation	1
		Sig. (2-tailed)	.
		N	21

*. Correlation is significant at the 0.05 level (2-tailed).

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