SIEMENS

SIMATIC

Process Control System PCS 7 Validation Support Manual I

Manual

This manual has the order number:
C79000-G7076-C736

Safety Guidelines

This manual contains notices which you should observe to ensure your own personal safety, as well as to protect the product and connected equipment. These notices are highlighted in the manual by a warning triangle and are marked as follows according to the level of danger:

Danger

indicates that death, severe personal injury or substantial property damage will result if proper precautions are not taken.

Warning

indicates that death, severe personal injury or substantial property damage can result if proper precautions are not taken.

Caution

indicates that minor personal injury or property damage can result if proper precautions are not taken.

Note

draws your attention to particularly important information on the product, handling the product, or to a particular part of the documentation.

Qualified Personnel

The device/system may only be set up and operated in conjunction with this manual.

Only **qualified personnel** should be allowed to install and work on this equipment. Qualified persons are defined as persons who are authorized to commission, to ground, and to tag circuits, equipment, and systems in accordance with established safety practices and standards.

Correct Usage

Note the following:

Warning

This device and its components may only be used for the applications described in the catalog or the technical description, and only in connection with devices or components from other manufacturers which have been approved or recommended by Siemens.

This product can only function correctly and safely if it is transported, stored, set up, and installed correctly, and operated and maintained as recommended.

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Siemens AG
Bereich Automatisierungs- und Antriebstechnik
Geschaeftsgebiet Industrie-Automatisierungssysteme
Postfach 4848, D-90327 Nuernberg

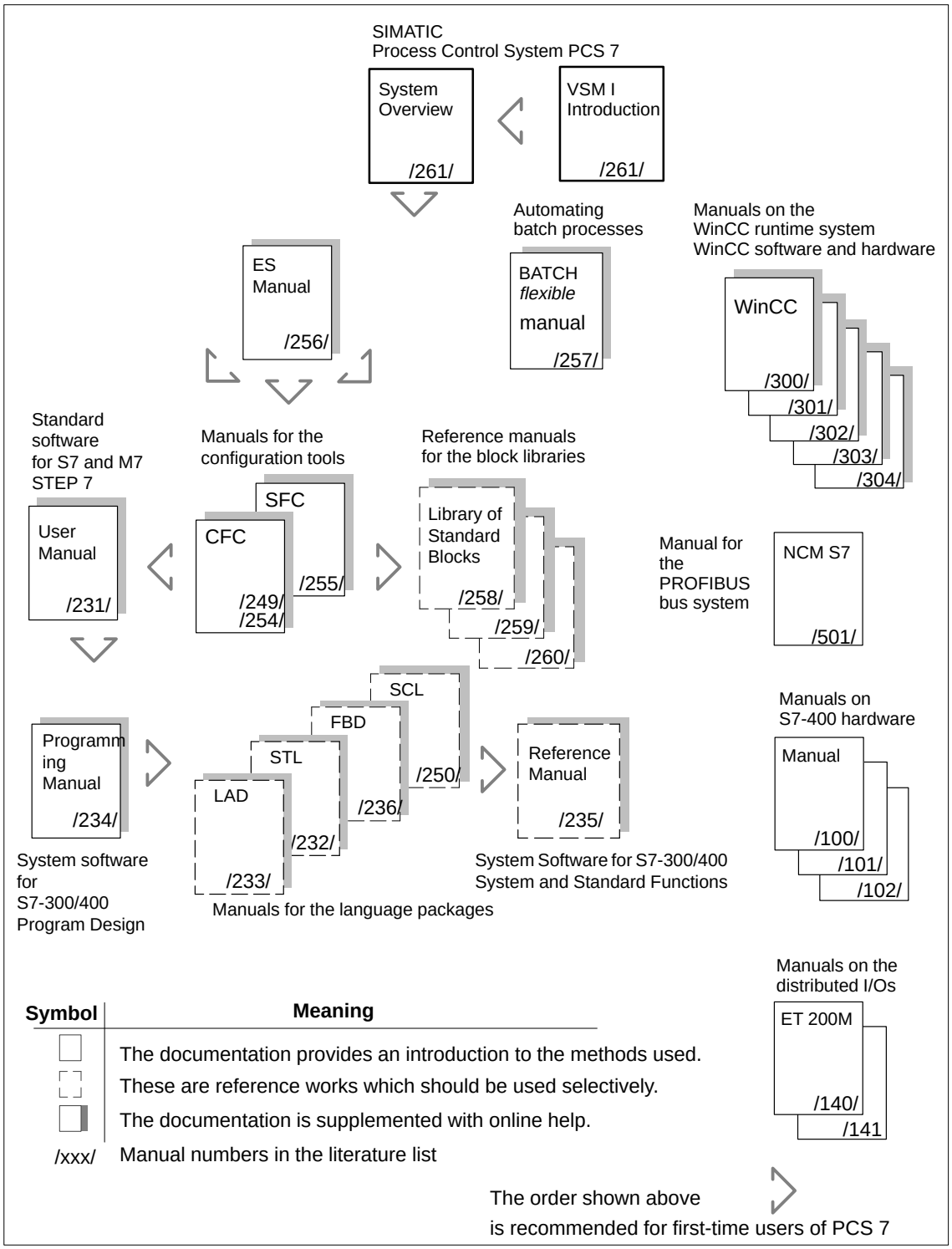
Disclaimer of Liability

We have checked the contents of this manual for agreement with the hardware and software described. Since deviations cannot be precluded entirely, we cannot guarantee full agreement. However, the data in this manual are reviewed regularly and any necessary corrections included in subsequent editions. Suggestions for improvement are welcomed.

Preface

Position within the Available Documentation (PCS 7)

There is a wide range of user documentation available to support you in configuring and programming an S7 programmable controller which is intended to be used selectively. The following explanations should make it easier for you to use the user documentation.



SIEMENS

VALIDATION SUPPORT MANUAL

Part I

General Guideline

PREPARED BY KEMPER-MASTERSON INC.

September 22, 1997

There exists in addition a

VALIDATION SUPPORT MANUAL

Part II

Validation Supporting Functions of SIMATIC PCS 7

This manual describes the technical Features of the Process Control System SIMATIC PCS 7 supporting the validation process and gives some SOP examples how to configure validation supporting features.

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1.0 INTRODUCTION

1.1 Objective

The objective of this manual is to target three audiences and their needs:

As a **client information document**, this manual is intended to give an in-depth view to validation aspects of computerized systems.
As a **client communication document**, it is intended to demonstrate the validation knowledge and cost effective working methods Siemens provides for regulated pharmaceutical projects. The objective is to facilitate better communications and relationships with the Sales, Projects and Support Services Teams. This document shows the phase model that may be used by applications in the regulated pharmaceutical industries and the mapping to SIEMENS procedures in the different roles described below. Included are the responsibilities of the different parties. Where appropriate, the responsibilities or value added services are highlighted by frames.

As an **internal reference document**, providing a uniform understanding throughout Siemens of Computerized System Qualification within the validation program for regulated Pharmaceutical applications. Providing a comprehensive reference with respect to the associated concepts, definitions, methodologies, and documentation requirements as they align with Siemens detailed procedures, specifications, protocols, records, and reports.

As a **training document,** to introduce validation issues and requirements to new employees and temporary, or contract, employees.

The manual identifies step-by-step the validation activities applicable to a process control system throughout a pharmaceutical manufacturer's project life-cycle, outlining the issues to be addressed by the client, and examining Siemens role and responsibilities as the „Supplier„ of standard components (SC Supplier), and system integrator (SI). There is also focus on optimizing validation activities by adopting best practice project management and engineering practices.

The validation methodology presented within this document, and subsequently endorsed by Siemens is consistent with that contained in the Parenteral Drug Association (PDA) Report on the Validation of Computer-related Systems. Other validation guidelines are recognized, and where applicable reference to documentation and material such as the Supplier Guide for Validation of Automated Systems in Pharmaceutical Manufacture, GAMP Forum / ISPE, and The APV Guideline „Computerized Systems„ based on Annex 11 of the EC Guideline 356, European Guide to GMP, is included.

1.0 INTRODUCTION (continued):

1.2 Scope

The focus is on pharmaceutical applications that are required to adhere to Current Good Manufacturing Practice (cGMP) in meeting the Code of Federal Regulations (CFRs) of the USA, and as inspected and enforced by the Food and Drug Administration (FDA).

The manual addresses each „phase„ of Validation as it applies to new applications of Siemens Process Control Systems, including the process management functions. Within the scope of validation for an entire, automated production plant / process, the process control system is only a component part (see Figure 1). This manual will assist the reader in understanding and generating the procedures, documentation and information necessary to qualify a process control system.

The manual does not include the qualification of the controlled function (e.g., process equipment) and associated operating procedures, or other systems not developed by Siemens.

The design, calibration, installation, maintenance and documentation of field instrumentation is not fully examined. However, for continuity and recognizing the relationship of sensors and other control instrumentation / devices to a process control system, an appropriate level of detail / reference is provided.

Where appropriate, examples specific to Siemens systems and services are identified.

1.0 INTRODUCTION (continued):

1.3 Background

1.3.1 What is Validation?

The FDA *Guideline on General Principles of Process Validation* defines validation to be, „Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.„ Validation is not new to the Pharmaceutical, Biopharmaceutical, Medical Device, and In-vitro Diagnostic industries. In fact, validation has been recognized since the mid 1970s. Only recently, in the past five to ten years, has validation received so much publicity, mainly due to the efforts of the FDA (issuance of *Guideline on General Principles of Process Validation*, 1987), drug and device manufacturers, associations such as the Parenteral Drug Association (PDA) (issuance of the Technical Report No. 18 on the *Validation of Computer-related Systems*), the Pharmaceutical Industry Computer Systems Validation Forum (PICSVF) and the International Society for Pharmaceutical Engineering (ISPE) (joint issuance of the Good Automated Manufacturing Practice, Supplier Guide, GAMP), and goals such as ISO 9000 Certification.

Validation is frequently viewed as an extension of Quality Assurance / Quality Control (QA/QC). QA/QC concepts have been implemented for many years by a wide variety of industries. Even though the terminology used and the practices implemented vary, many parallels can be identified between industries. In addition, the ultimate goals are the same; high quality components and services at competitive prices.

The Pharmaceutical, Biopharmaceutical, Medical Device, and In-vitro Diagnostic industries are required to take these goals a step further in that validation of all quality critical components involved in the control and manufacture of drug products and drug substances is required in both general and specific terms by cGMP regulations and guidelines. Further, and to protect the public, national regulatory authorities such as the FDA. exist to issue and enforce regulations and guidelines that either directly or indirectly address the identity, purity, strength, and efficacy of drug products and medical devices. The main theme of these regulatory documents is to build quality into the component, not to test quality into the component. In other terms, component quality should not be an afterthought or retrospective. Thus validation needs to be integrated into every phase of a system development life cycle, including the planning, definition, design, construction, installation and testing work processes. Validation ensures the following questions are addressed:

- Are the processes adequate?
- Are the processes consistent and reproducible?
- Are the processes well documented?
- Are the processes based on solid scientific rationale?
- Do the processes minimize or eliminate the potential for error?
- What process/methodology related factors affect the product or device?
- What personnel-related factors affect the product or device?
- What materials-related factors affect the product or device?
- What equipment and systems affect the product or device?

All validation activities must be performed in accordance with predefined protocols / procedures.
When validation activities have met the protocol / procedure requirements, and have been documented and approved, the computer system will be certified as validated.

1.0 INTRODUCTION

1.3 Background (continued):

1.3.2 Who must Validate?

Manufacturers of drug products [pharmaceutical and biopharmaceutical (human and veterinary)], medical devices, and in-vitro diagnostics must qualify their processes/methodologies, materials, personnel, and equipment/systems for use in regulated processes.

Regulatory authorities such as the FDA do not validate systems, but are charged with inspecting the validation documentation provided by the pharmaceutical manufacturer. From this documentation, the FDA assess that an automated manufacturing process will consistently produce a quality product to its specification.

1.0 INTRODUCTION

1.3 Background (continued):

1.3.3 Why Validate?

Reason No. 1: cGMP Compliance

One reason why companies validate is to ensure compliance with the Food and Drug Administration's current Good Manufacturing Practices (cGMPs) sections 21 CFR-210, 211and Part 11, and 21 CFR-820 as they apply to validation. In addition, compliance with the Food and Drug Administration's *Guideline on General Principles of Process Validation,* 1987 is recommended. It is the responsibility of both Siemens and its clients to know, understand, and comply with cGMP regulations and guidelines as they apply to their specific needs.

For the pharmaceutical manufacturer the following general compliance expectations must be met during Computerized System qualifications:

Computer systems which control or document pharmaceutical processes, laboratory activities, inventory transactions, or critical manufacturing support services must be validated.

A written, comprehensive procedure must be available which describes in sufficient detail the objectives and procedures of the validation program and sets forth authorities and responsibilities.

Prospective validation shall consist of main validation phase approvals by means of Specification Reviews, Design Reviews, Installation Qualification(IQ), Operational Qualification(OQ), Performance Qualification (PQ) and On-going Evaluation.

Retrospective validation may be conducted if sufficient historical data are available, i.e. historical data, problem logs, change control records, test and calibration records.

Validation must be conducted according to written and approved Protocols.

Procedures shall be implemented to operate and maintain the system in its validated state.

Details of the validation shall be contained in a validation summary report which is reviewed and approved by authorized personnel.

Below are examples related to application of computer control systems:

Example No. 1: Section 501(a)(2)(B) of the Food, Drug, and Cosmetic Act

Provides that a drug shall be deemed to be adulterated if the methods used in, or the facilities or controls used for, its manufacturing, processing, packaging, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirement of the act as to safety and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess. The failure to comply with any regulation set forth in GMP 211 through 226, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.

1.0 INTRODUCTION

1.3 Background

1.3.3 Why Validate? (continued):

Example No. 2: Section 21 CFR 211.68 of the cGMPs

(a) Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily, may be used in the manufacture, processing, packaging, and holding of a drug product. If such equipment is used, it shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained.

(b) Appropriate controls shall be exercised over computer or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. A backup file of data entered into the computer or related system shall be maintained except for certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to assure that backup data is secure from alteration, inadvertent erasures, or loss shall be maintained.

Reason No. 2: Cost of Quality

As stated in FDA's *Guideline on General Principles of Process Validation*, a specific process must consistently produce a product meeting its pre-determined specifications and quality attributes. By performing validation activities, one is actually assuring the consistent functionality of the equipment/system and therefore the consistent quality of the product being manufactured. In addition, the costs associated with the quality of the product can be balanced. Four main Quality Cost categories are listed below:

Prevention Costs are costs associated with the prevention of product failures :
Quality Planning
Supplier Certification Program
Documentation
Calibration
Testing
Validation
Consulting Services
Quality Assurance Auditing and Inspections
Employee Training
Preventive Maintenance
Failure Rectification

1.0 INTRODUCTION

1.3 Background

1.3.3 Why Validate? (continued):

Data Acquisition, Analysis, and Reporting
Application of Proven System Configuration to Other Projects
Improving / Optimizing Processes, Automation, Plant Layout
Supplier Evaluation/Selection
Policies and Plans

Appraisal Costs are costs associated with evaluation activities such as:

Evaluation of Materials (Raw / In-process / Finished / Packaging)
Evaluation of In-process Materials
Evaluation of Finished Products
Evaluation of Stability Samples
Process Data Analysis
Environmental Data Analysis
Utility Monitoring

Internal Failure Costs are costs associated with materials that do not meet their predetermined specifications and quality attributes such as:

Yield Losses (Rejects/Culls, Reworks, Retests, Scrap)
Equipment/System Downtime
Troubleshooting/Debugging

External Failure Costs are costs associated with finished products that do not meet their predetermined specifications and quality attributes such as:

Product Recalls
Product Returns
Lost Potential Business
Consumer Complaints
FDA Seizures and Injunctions

1.0 INTRODUCTION

1.3 Background

1.3.4 Where does the Supplier fit in?

Regulatory authorities such as the FDA, have three major concerns regarding computer validation**:**

1. Does the system perform accurately and reliably?
2. Is the system secure from unauthorized or inadvertent changes?
3. Does the system provide adequate documentation to support the assertion that it is qualified for use in validated processes?

With this in mind there is emphasis on the following system (data) issues:

- controls
- security
- integrity
- traceability
- repeatability

…….and how this is achieved through structured and documented methods and reports.

Siemens as a supplier to FDA-regulated industries recognizes the manufacturer's need to successfully qualify computerized systems used in the support of manufacture / distribution of drug products, and to ensure that no assumptions are made with respect to the accuracy and dependability of the computerized systems used in support of regulated processes. For this, the following key client requirements are to be met:

- Plan and implement computer systems efficiently and for minimum long-term costs.
- Design for consistently accurate and reliable operation.
- Regulatory Compliance.
- Reduce exposure to loss of expertise / knowledge by documenting system development, application design, status, changes, qualification and maintenance.
- Minimize risk to system development, design and maintenance by conducting these activities in accordance with approved written procedures.

Siemens as a supplier of Process Control System Components and Systems Integration Services, is committed to providing systems and services of the highest quality. Siemens accepts its responsibility to ensure that installed systems and support services meet or exceed contracted client requirements.

This is accomplished through a consistent and auditable high quality approach to the design, development, installation, commissioning, calibration, and maintenance of Siemens systems supported by comprehensive and accurate documentation. In addition, the availability and quality of training for Siemens and client personnel plays an essential role.

1.0 INTRODUCTION

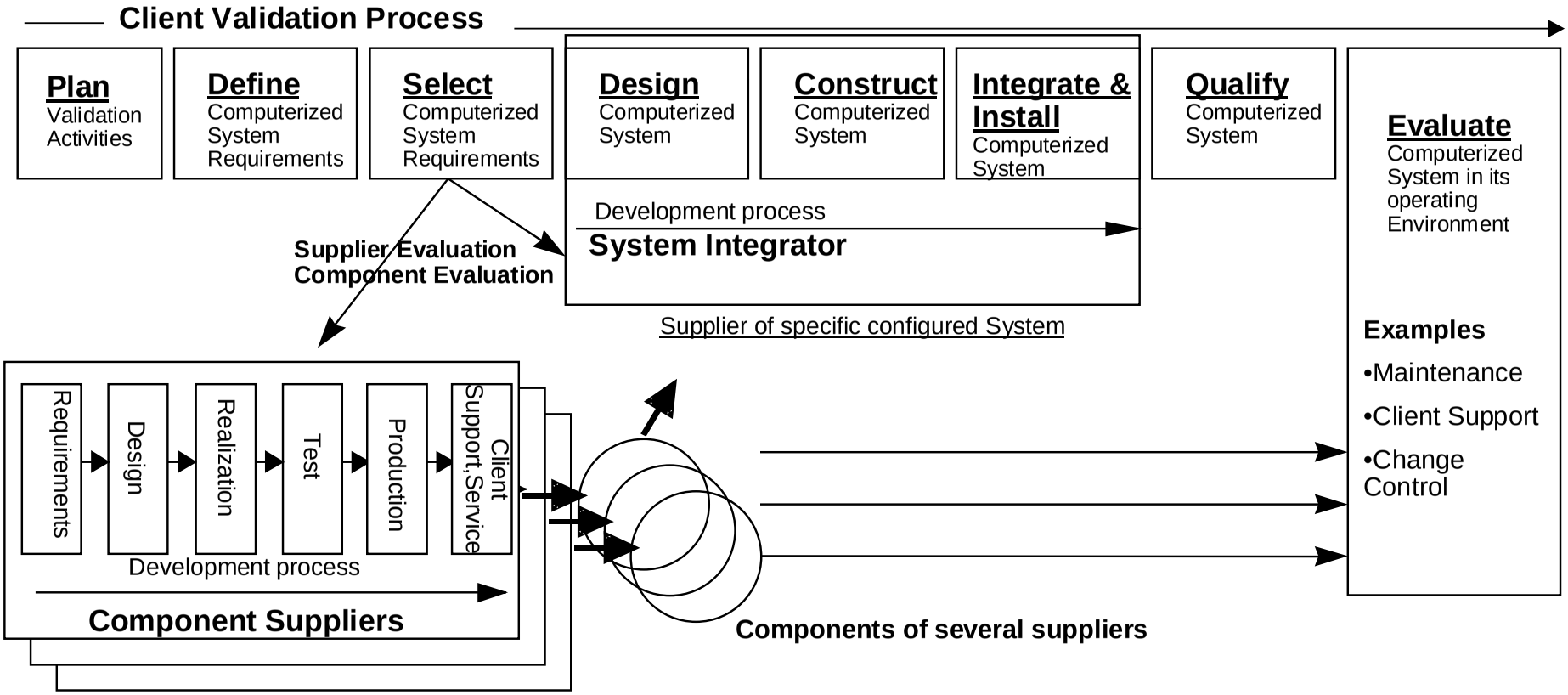
1.3 Background

1.3.4 Where does the Supplier fit in? (continued):

Clients depend on Siemens to understand the pharmaceutical manufacturing environment and constraints, and to deliver its systems and services in a manner which facilitates effective and efficient system validation, operation, maintenance upgrade and change control. Clear, concise, and accurate documentation throughout all phases enables preparation of validation documentation and reduce deviations identified during qualification testing.

Figure 1 provides a basic representation of the roles and responsibilities of the Component Supplier (Siemens), Systems Integrator (Siemens or third party), and client.

Figure 1: **Influence of the Client Validation Process on Component Suppliers and the System Integrator**



1.0 INTRODUCTION

1.3 Background

1.3.5 Responsibility Overview

In the sections which follow, a validation methodology is presented. For each step in the process (see Section No. 3.1.1), documentation requirements and Siemens responsibilities are defined. Within clause 3 the responsibilities are highlighted with a frame so that it can be better identified against a general information about suppliers.

It should be noted that FDA-regulated clients are ultimately responsible for regulatory matters within their facilities, including satisfying all validation needs.

However, Siemens can support client needs by providing validation-related services either as a standard of practice, or as additional value-added (additional cost) services, available upon request.

In complying with the methodology recommended in Section No. 3.1.1, the main responsibilities of the FDA-regulated manufacturer in addressing a computerized system qualification include (at a minimum):

1. Select Validation Team
2. GMP Compliance and Risk Assess the Project / System
3. Produce Review and approve a Validation Project Plan
4. Produce, Review and Approve a Project and Quality Plan
5. Produce, Review and Approve the computerized system User Requirement Specification
6. Verify Critical Process Data and Test Criteria
7. Produce, Review and Approve the Validation Document Matrix
8. Conduct and Approve the Requirements Specification Review
9. Audit and Select Supplier
10. Review and Approve the Supplier’s Quality Plan
11. Review and Approve the Computer System Design Specifications
12. Monitor Development of the System
13. Review and Approve System Acceptance Tests
14. Conduct and Approve the Design Review

1.0 INTRODUCTION

1.3 Background

1.3.5 Responsibility Overview (continued):

15. Produce and Approve the Qualification Protocols for IQ, OQ
16. Conduct, Report and Approve IQ, OQ
17. Produce and Approve the PQ Protocol
18. Conduct, Report and Approve Performance Qualification (PQ)
19. Produce and Approve the Final (Validation) Report
20. Develop and Maintain a Training Plan
21. Review and maintain Validation Status (by Periodic Review, Change Control, Deviation Control, Maintenance Procedures, Document Control)

Although the responsibility for validation remains with the pharmaceutical manufacturer, the supplier will normally have considerable involvement in activities 10, 11, 12, 13, 14, 15 and 16 identified above. Further, and depending on the extent of contracted services, the Supplier may also have substantial involvement in activities 17, 18, 19, 20 and 21.

APPENDIX NO. 2 identifies the key validation documentation to be produced throughout the validation project Life-cycle, and the Client / Supplier responsibilities pertaining to the provision and management of the documents.

Siemens have a management system and project methodology / procedures which will ensure system qualification meets the regulated - client's validation requirements. To undertake system implementation the Supplier must ensure they have suitable expertise and adequate resources in order to support the validation program.

It is recognized that a certified Quality Management System supports GMP compliance and validation goals, and as such the Supplier's quality procedures are key to the pharmaceutical manufacturer's validation program.

An area which may require supplier involvement is „compliance and risk assessment„ (see 1 above). Risk analysis should investigate and assess the direct and indirect effects of the computerized system on product quality and GMP. Every function stipulated in the client's requirements and performed by the computerized system should be investigated and assessed to ensure the processes and product conform to specifications.

1.0 INTRODUCTION

1.3 Background

1.3.5 Responsibility Overview (continued):

As part of this exercise all quality critical data should be identified, especially data which needs to be controlled by restricted access within the computerized system.

Siemens will not necessarily be involved with the initial compliance and risk assessment exercise which is normally conducted pre-supplier selection. However, after the process control system and system integrator are chosen the functionality provided by that system in performing its designated tasks should be examined in more depth. This will follow a formal procedure and normally be a joint exercise between the client manufacturer (or their representative) and the supplier and may even be conducted as part of the supplier(s) audit.

Tables 1 and 2 provide more specific information regarding responsibilities of the Component Supplier (Siemens AUT) and System Integrator (Siemens or third party) throughout the validation process presented in Section No. 3.1.1. Also included are references to corresponding services, procedures, deliverables, and other documentation which currently exists at Siemens.

1.0 INTRODUCTION

1.3 Background

1.3.5 Responsibility Overview (continued):

Table 1: Component Supplier (AUT)

Steps in Qualifying	Validation Step	Interpretation & Responsibilities	Responsible Siemens Group(s)	Siemens Policies	Siemens SOPs	Other Supporting Documentation	Siemens Deliverables[1]
Design Component & System	Functional Design Spec.	Marketing Research & Analysis	• AUT V19&AUT S14	AUT 1Q	VA 502-000		
	Computerized System Specification	• System Architecture	• AUT S18	AUT 1QM-Manual Part „Regelwerk für …„			• Software-Architecture • System Specification
		•	• AUTS11/S12 & AUT91		VA S502-030 Produktdefinition		• Component Reqt paper(s)
	Computer System Specification	• Specification	• AUT1E & AUT91 & AUT93	AUT1Q	VA502 -000		• Component Specification(s)
	Design HW	• Design	• AUT 1E & AUT91 & AUT93		VA502-002		• Optional Component Design Specifications
	Design SW	• Design	• AUT 1E & AUT91 & AUT93		VA 502 -001		• Optional Component Design Specifications
Construct Component & System	Construct & Test Hardware	• Realization	• AUT1E & AUT91 & AUT93	AUT1Q	VA502 -002		• Component Prototype
	Develop & Test Software	• Realization	• AUT 1E & AUT91 & AUT93	AUT1Q	VA502 -001		• Component Prototype
	Integrate & Test Computer System	• Documentation (Manual) • Integration • Integration Test	• AUTE14&AUT91& AUT93 • AUTE111&AUTE14& AUT91		VA E507-600,-602,-603		• Prototype

[1] Only for Siemens internal use

1.0 INTRODUCTION

1.3 Background

1.3.5 Responsibility Overview (continued):

Table 1: Component Supplier (AUT) (continued)

Steps in Qualifying	Validation Step	Interpretation & Responsibilities	Responsible Siemens Group(s)	Siemens Policies	Siemens SOPs	Other Supporting Documentation	Siemens Deliverables
Integrate & Install System	Integrate & Install Computerized System	• System Test • Production • Product Shipping	• AUT E14 • AUT EWK/EWA • AUT 1 LOG	AUT1Q AUT1Q AUT1Q	VA E507-600,-603,-604 VA E508-600 PB001-PB830 AR505-1+511-1+511-2+51		• System Test Profile[1] • Component[1] • Component Inventory[1]
	Commissioning	N/A					
Qualify System	IQ	N/A	N/A				
	OQ	N/A	N/A				
Evaluate System	PQ	N/A					
	Ongoing Evaluation	• Customer Support • Maintenance	• AUT 1CS	AUT1 Q	VA C516-002 VAC520-001 VA C520-010		• Hotline

[1] Only for Siemens internal use

1.0 INTRODUCTION

1.3 Background

1.3.5 Responsibility Overview (continued):

Table 2: System Integrator (SI)

Steps in Qualifying	Validation Step	Interpretation & Responsibilities	Responsible Siemens Group(s)	Siemens Policies	Siemens SOPs	Other Supporting Documentation	Siemens Deliverables
Plan	Validation Policies & Procedures		• AUT 1			VSM	
			• VPP	• Validation Plan Support • Quality Plan	• AUT V38		• Validation Plan • Qual Plan
Define Functional Requirements	Operation Reqt spec Support		• AUT 38 V with the help of ANL A4				• Operation Reqt Spec
	System Requirements		• AUT 38 V with the help of ANL A4				
	Computerized System Reqt.	• PQ Protocol Dev Assistance					• Draft PQ Protocol
Select	Supplier Evaluation	External Audits	• AUT 38 V • AUT3 (QA)				
	Product Evaluation						
	Select Comp System	N/A	N/A				
Design Application	Functional Design Spec.	• M&C Reqts Spec Support	• AUT 38 V with the help of ANL A4				• M&C Reqts Spec.
	Computerized System Specification	• Order Spec Support	• AUT 38 V with the help of ANL A4				• Order Spec
	???	• OQ Protocol Dev. Support	• AUT 38 V with the help of ANL A4				• Draft OQ Protocol
	Computer System Specification	• Control System Detail Specifications	• AUT 38 V with the help of ANL A4				• Spec.
	Design HW	• Design Hardware	• AUT 38 V with the help of ANL A4				• Detail HW Design
	Design SW	• Design Software • IQ protocol Dev Support	• AUT 38 V with the help of ANL A4				• Detail SW Design • Draft IQ Protocol

1.0 INTRODUCTION

1.3 Background

1.3.5 Responsibility Overview (continued):

Table 2: System Integrator (SI) (continued)

	Validation Step	Interpretation & Responsibilities	Responsible Siemens Group(s)	Siemens Policies	Siemens SOPs	Other Supporting Documentation	Siemens Deliverables
Construct Application	Construct & Test Hardware	• Manufacture Construction HW Module & Intg Test	• AUT38 with the help of ANL A4				• ? Test Report
	Develop & Test Software	• Programming/Config of Cont. sys. SW	• AUT38 with the help of ANL A4				
		• Module Test	• AUT38 with the help of ANL A4				• Test Report
	Integrate & Test Computer System	• SW Module & Integration Test	• AUT38 with the help of ANL A4				• FAT Report
Integrate & Install System	Integrate & Install Computerized System	• Onsite IQ Protocol Dev Support	• AUT38 with the help of ANL A4				• System Test Profile
		• Installation & Cabling	• AUT38 with the help of ANL A4				
		• SW Installation	• AUT38 with the help of ANL A4				
	Commission	• Commissioning of Control System	• AUT38 with the help of ANL A4				• Component Inventory
		• Loop Checks	• AUT38 with the help of ANL A4				
		• IQ protocol Execution Support	• AUT38 with the help of ANL A4				• As-built documentation CommissReport
		• OQ Protocol Execution Support	• AUT38 with the help of ANL A4				• IQ Protocol • OQ Protocol
Qualify	IQ	• IQ Protocol Execution Support	• AUT38 with the help of ANL A4				• IQ Report
	OQ	• OQ Protocol Execution Support	• AUT38 with the help of ANL A4				• OQ Report

1.0 INTRODUCTION

1.3 Background

1.3.5 Responsibility Overview (continued):

Table 2: System Integrator (SI) (continued)

	Validation Step	Interpretation & Responsibilities	Responsible Siemens Group(s)	Siemens Policies	Siemens SOPs	Other Supporting Documentation	Siemens Deliverables
Evaluate	PQ	• PQ Protocol Execution	Finalizations				• PQ Protocol • PQ Report
	Ongoing Evaluation	• Change Control/Updating Documentation • Maintenance • Calibration	Finalizations				

2.0 VALIDATION CONCEPTS

Although the GMPs define what controls should be in place, they do not say how to implement those controls. Individual and collaborative efforts by the Pharmaceutical industry and their specialist Consultancies, the Regulatory Authorities, and Suppliers have over the years produced guidance on methods (and support documentation) on how to conduct the required controls and ensure successful validation. For validation the qualification of a Computerized system involves three main steps:

- Defining a written validation plan
- Generating documentation of activities (signed and dated) to provide evidence that the plan is followed
- Providing a documented process to monitor and control change

However, the size and complexity of the validation task can appear anything but simple. A logical, modular approach makes validation more manageable. The recognized approach is based on a system life-cycle, as described in Section 3.1.1. Most pharmaceutical companies use this approach as the basis for their validation programs, including computerized system qualification.

2.0 VALIDATION CONCEPTS (continued):

2.1 Process Validation

2.1.1 Prospective Validation

2.1.2 Retrospective Validation

The FDA *Guideline on General Principles of Process Validation* defines validation to be, "establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes." According to current interpretation, validation is the entire procedure of establishing the required documented evidence. To avoid confusion, the term, "validation," should not be used for any specific type of testing or protocol.

The term „process„ is not restricted to a manufacturing process. It may be a laboratory process, a document control process, a data management process, or any other process requiring validation.

In FDA's *Guideline on General Principles of Process Validation*, there are two recognized types of Validation:

2.1.1 Prospective Validation

Prospective Validation is "validation conducted prior to the distribution of either a new product, or product made under a revised manufacturing process, where the revisions may affect the product's characteristics."

2.1.2 Retrospective Validation

Retrospective Validation is "validation of a process for a product already in distribution based upon accumulated production, testing and control data."

2.0 VALIDATION CONCEPTS (continued):

2.2 Computerized System Definition

For the purposes of this manual a "system" is defined as:

"Any programmable device including its software, hardware, peripherals, procedures, users, interconnections and inputs for the electronic processing and output of information to be used for reporting or control."

This term describes a broad range of items including automated manufacturing equipment, process control systems, automated laboratory equipment, manufacturing execution systems and computers running laboratory or manufacturing database systems.

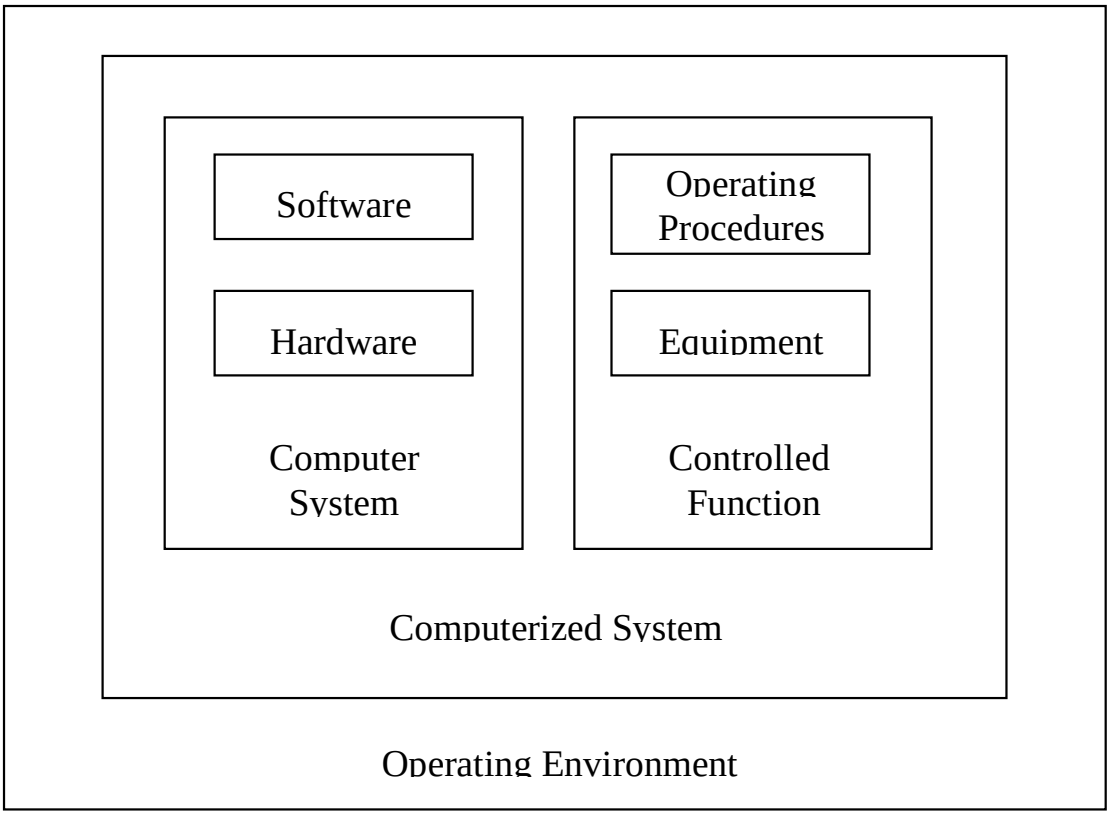
Hence, a Computerized System is a system controlled partially or totally by a computer. It usually comprises of a process or operation integrated with a Computer System.

The Computerized System is made up of a Computer System and the Controlled Function. A Computer System is composed of the computer hardware, including all of its peripherals, and the software components to perform a specific function or group of functions. The Controlled Function is composed of the equipment and / or manual operations which are to be controlled and the operating procedures defining the function of that equipment or manual operation.

The Computerized System operates in an Operating Environment, which is a term describing a defined integrated work flow (procedures) between people and computerized systems, to accomplish a specific task. The Operating Environment includes information input from operators or other sources, input of material to be processed, documentation, the physical environment, plant support utilities, and any other factors that might affect the state-of-control of the Computerized System. The Operating Environment can also encompass work environments which utilize more than one computer system to accomplish a complete work operation.

Figure 2 provides a pictorial representation of a Computerized System.

Figure 2: Computerized System Arrangement



2.0 VALIDATION CONCEPTS (continued):

2.3 Computerized System Qualification

Aligning with the definition of Process Validation as closely as possible, Computerized System Qualification can be defined as, "establishing documented evidence that provides a high degree of assurance that a specific Computerized System will consistently operate in accordance with pre-determined specifications."

It is important to introduce the concept of Computerized System Qualification (and both the component Computer System and Controlled Function Qualifications) in addition to that of Process Validation; this because some systems that must be qualified are not directly involved in the processing of a product. Even in systems that are so involved, it is often desirable to distinguish between the qualification of the system and the overall validation of the process of which it is an integral part.

The quantity of documentation required to achieve a „high degree of assurance„ is subjective and is usually determined by experience and good engineering practice. Most documentation required for validation should be generated as part of the implementation of a well planned project.

A Computerized System cannot be qualified unless it is performing its intended function in its Operating Environment and the process it is executing can be validated.

3.0 VALIDATION METHODOLOGY

3.1 Validation Planning

The initial activities of planning for the pharmaceutical manufacturer include identifying GMP critical systems, validation policies, validation SOPs, and defining activities, procedures and responsibilities for establishing the performance adequacy of a system.

To support pharmaceutical manufacturing clients, Siemens has developed a validation methodology based on the following recognized models, and thus provide a Prospective Validation approach for the new application of computerized systems:

PDA Technical Report No. 18, Figure 3 - Steps in Validating Computer-Related Systems.

GAMP / ISPE, Supplier Guide for Validation of Automated Systems in Pharmaceutical Manufacturing, Figures 2, 3 and 4 , Life-cycle and „V„ Plan Models.

(The validation methodology to be followed for existing systems and processes, i.e. Retrospective Validation, will have many similar activities, but puts emphasis on assembly of appropriate historical data in order to facilitate the process of defining and documenting the required system specifications and assessing the extent of re-testing and qualification that would be necessary. Regulatory Authorities expect all new systems, even those of 3 /5 years old to have been undertaken under Prospective Validation. Consequently Retrospective Validation is not covered in this manual).

The validation planning and implementation techniques used by Siemens support the Life-cycle approach to Computerized System application.

3.0 VALIDATION METHODOLOGY

3.1 Validation Planning (continued):

3.1.1 Life-Cycle Approach

Life-cycle Approach

The validation methods supported by Siemens are illustrated in, Figure 3, Steps in Qualifying a Computerized System, and further detailed in Sections 1.3.4 and 1.3.5 of this manual. The Life-cycle methodology aligns validation requirements closely with Siemens project execution procedures. The validation process is subdivided into individual steps. Each step will provide specific deliverables. A verification strategy will be defined for each step, where the deliverables or outputs are checked against the inputs or requirements. During each step, documentation is generated that forms the basis for future steps.

The validation model identifies the steps of developing, implementing and operating of automation software (SW) / hardware (HW) and field instrumentation (devices) that normally comprise a computerized system in the pharmaceutical manufacturing GMP environment:

Steps in Validating Computerized Systems:

1. Planning
2. Definition
3. Select Supplier(s)
4. Design
5. Construct (system build)
6. Integrate and Install
7. Qualify
8. Evaluate

The life cycle implies a top down process where a defined system is broken down into sub-systems and modules, followed by a process of integration into the final tested product. All requirements, activities and stages of the process being documented and approved.
The prime input into the life cycle is the User Requirement Specification (URS), for which a corresponding Functional Design Specification (FDS) is required to describe how the intended system will meet the stated requirements. The FDS is the basis for design specifications for all elements of the system. System testing procedures are derived from the system design specifications.
To control and document satisfactory completion of each validation step a structured qualification must be conducted. These key activities include Specification Review, Design Review, Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ). On-going Evaluation of the system provides confirmation of the validation status of the system throughout its operational life. Test procedures that are necessary to support qualification must be developed to address the requirements and acceptance criteria of each specification.

3.0 VALIDATION METHODOLOGY

3.1 Validation Planning

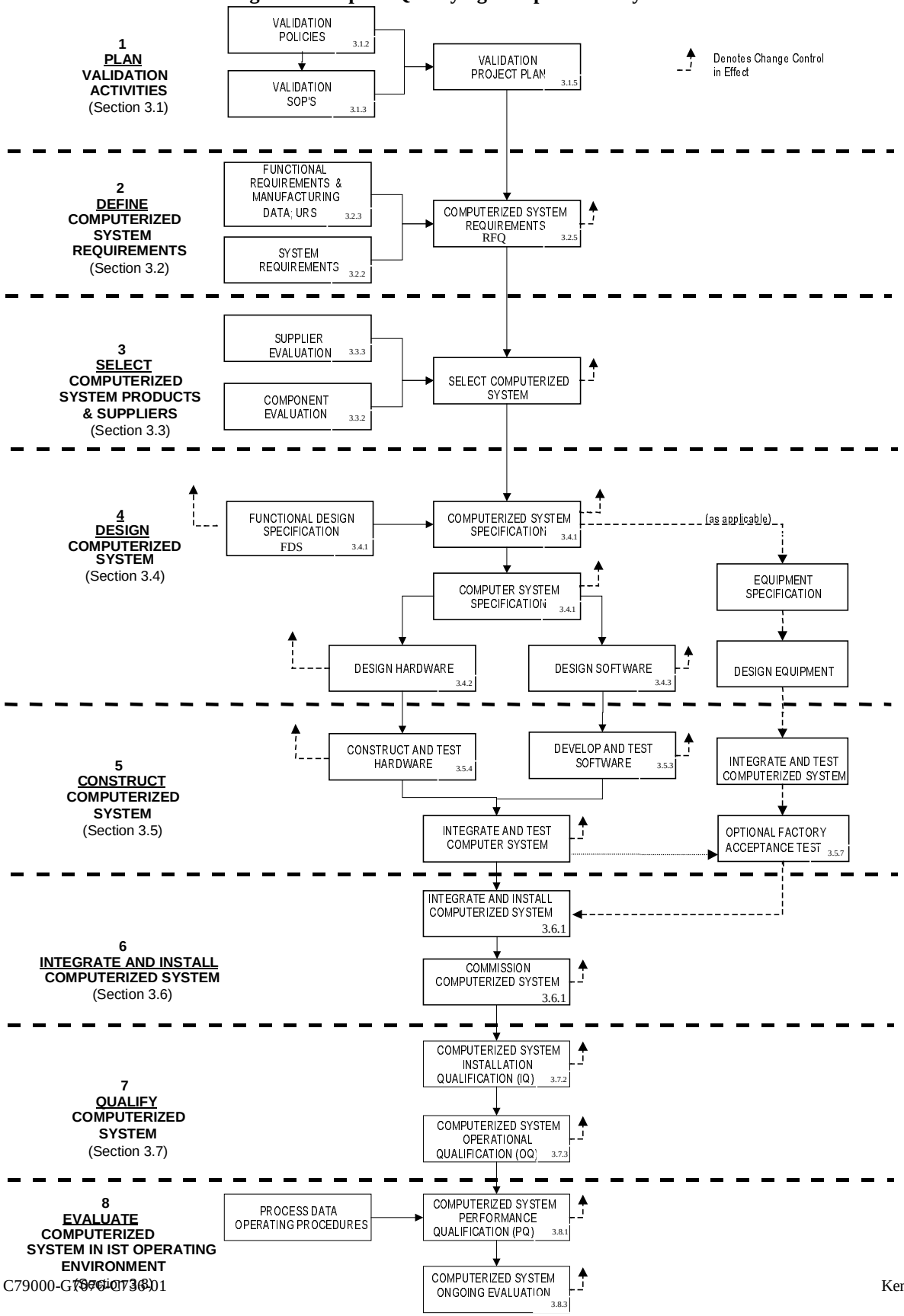
3.1.1 Life Cycle Approach (continued):

Outline of Software / Hardware Development and Testing

The Software (SW) and Hardware (HW) configuration of the process control system is based on the computerized system design specifications. Using top-down definition, the primary process steps are first identified; these are then successively sub-divided into operations and phases which are assigned to equipment modules and tag numbers. The relationship between process stages and the individual parts in the production plant (units, equipment, control modules) should also be described.

The software and hardware are realized in two stages. Using a 'bottom-up' design method, the suitability and utilization of standard function blocks is determined, and any non-standard functions / control function blocks are defined and developed. The next stage involves linking the project specific function blocks and standard function blocks together to form more powerful functions and sequence and recipe controls which may be documented in the form of flow diagrams, continuous function charts, etc. The same is done with the hardware configuration, from the individual components right up through the system architecture and topology. While designing the software and hardware all levels of integration are defined so that corresponding test levels can be developed at the appropriate time.

Figure 3: Steps in Qualifying Computerized Systems



3.0 VALIDATION METHODOLOGY

3.1 Validation Planning

3.1.1 Life Cycle Approach (continued):

Overview of Qualification

The qualification and testing of a computerized system is performed at several levels. The installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ) activities are when review and testing is carried out on the system design specification(s), functional design specification and user requirement specification respectively (see Figure 3). Qualification documents need to reference original specifications which define what needs to be tested. Therefore , the tests are derived from, and correspond to the earlier specification phases. Test procedure definition includes acceptance criteria and expected results.

It is recommended that these test procedures are written following the completion of specification and that they reference directly the requirements / functions / expected results in the respective specification. This will best ensure all requirements are addressed, acceptance criteria met and enable appropriate test execution and reporting. It is also advisable to conduct on-going review of the test plans in parallel with the software / hardware development; this to capture further test considerations / details and ensure comprehensive testing.

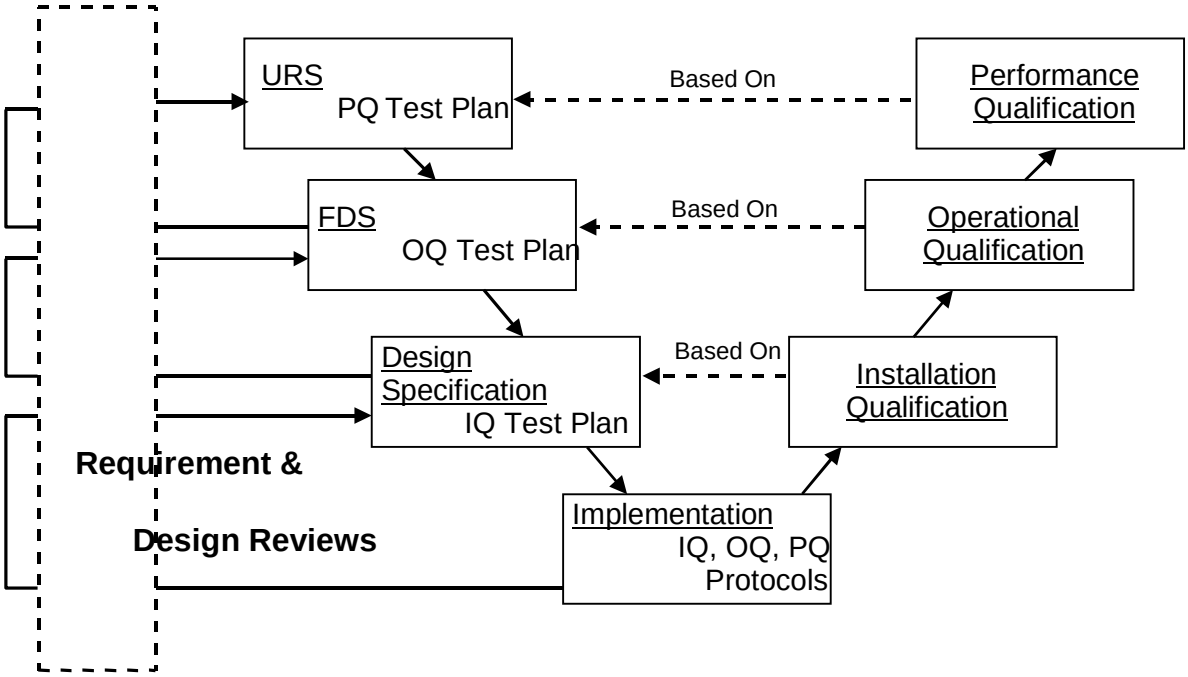
The V-Plan shown below illustrates the direct relationship of testing to each level of specification, where the left arm of the „V„ defines what the system should do and the right arm, the process that provides assurance that it does what is intended.

3.0 VALIDATION METHODOLOGY

3.1 Validation Planning

3.1.1 Life Cycle Approach (continued):

Figure 4: The Qualification Model



The Phase Model

All activities throughout the Design, Construct, and Integrate and Install steps, including documentation preparation conducted in line with the following phase model. This methodology enabling appropriate verification and traceability to control work and aid validation, and forms the basis for the supplier to execute a pharmaceutical manufacturing project.

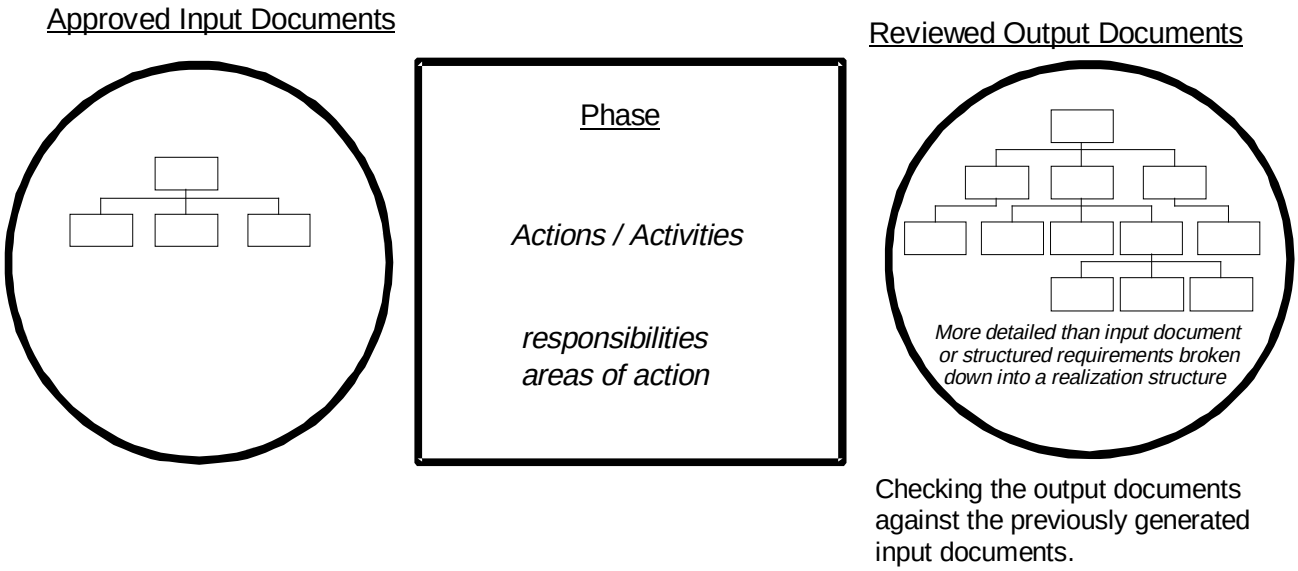
The phase model is represented as a simplified network plan; all procedural / phase results are documented. Phases have input documents, which are the basis for producing the output documents. These are to be produced during the phase and reviewed at the end of it. This approach enables effective cross reference from initial requirements to design specification, and through to acceptance testing and qualification (see 3.1.1.).

3.0 VALIDATION METHODOLOGY

3.1 Validation Planning

3.1.1 Life Cycle Approach (continued):

Figure 5: Phase Model



3.0 VALIDATION METHODOLOGY

3.1 Validation Planning (continued):

3.1.2 Validation Strategy

GMP-regulated clients will have written and approved high level Validation Policies in place that communicate management's expectations and that need to be followed for any validation project. Validation Policies are intended to establish responsibilities and expectations and do not specify specific testing requirements.

Validation Policy

A pharmaceutical manufacturer will have a Validation Policy statement approved by management and documenting their commitment to validate their products and associated processes. Respective Computerized Systems will be included and will typically be covered as follows:

The focus of the computerized systems validation activity will be to ensure that all the quality critical computerized systems perform consistently to the required standards.

Validation will be integrated into every phase of a system development life cycle, including the design and development phases.

During the procurement of new computerized systems, validation requirements and costs must be considered as part of the capital approval process.

There will be a Master Validation Plan which summarizes key validation activities on the site and which must include computer systems. This document will normally be approved by the Site Manager.

The requirements for performing a computerized system qualification should be documented in a procedure.

All validation activities will be performed in accordance with predefined protocols.

When validation activities have met the protocol requirements and have been documented, the computerized system will be certified as qualified.

Where validation activities do not meet the defined acceptance criteria in the protocol and in any protocol supplements raised during the validation, the computerized system will not be regarded as qualified under the validation plan.

An on-going validation evaluation regime must be in operation, incorporating change control and periodic review of the validation status.

3.0 VALIDATION METHODOLOGY

3.1 Validation Planning

3.1.2 Validation Strategy (continued):

Validation Organization

An organizational structure will be established to facilitate the qualification of all computerized systems. A Validation Master Plan will be developed and the activities will be tracked for conformance to the plan. Individual validation projects will be managed and performed by the relevant personnel drawing representatives from the following functions dependent on the nature of the system:

- Quality Management
- Information Technology
- Engineering
- Owner Department

For validation projects involving external suppliers, representation of the computerized system supplier, engineering contractor and system integrator would normally be expected on commencement of the respective contract. The Purchasing / Contracts groups also play a key role in administering contractual validation activities and documentation.

Computer System Inventory and Application Assessment

An inventory will be set up to capture all computerized systems at a site; systems will have to be assessed to determine whether validation is required, and if this is the case, a compliance and risk assessment evaluation performed. This applies to all planned or existing computerized systems.

Validation Master Plan

Validation Master Plans cover process, facility, utility and those computerized systems identified as requiring qualification, documents, responsibilities, priorities, and the intended schedule. It describes the company validation methodology, and outlines GMP and validation training programs approved by the pharmaceutical manufacturer (see APPENDIX NO. 1A).

These plans may be consolidated into one site master plan or separate plans, e.g. there may be one plan for processes, another for facilities / utilities, and another for computerized systems. The plan should include all areas / systems for which validation is planned and define the status of each area, providing a broad indication of when validation is to be completed.

For computerized systems the Validation Master Plan describes the site and its computerized system applications, identifies any regulatory aspects of systems or sub-systems, indicates system(s) validation status, and where a system or sub-system is not qualified the expected completion date.

The plan should be reviewed annually to ensure that it is current, and that progress is being made against the plan. The application of new systems will generate new and additional requirements to be identified.

Siemens does not routinely participate in the preparation high level Validation Policies and Plans for the client. However, if a client requested assistance, then Siemens may participate as a value-added service.

3.0 VALIDATION METHODOLOGY

3.1 Validation Planning (continued):

3.1.3 Standard Operating Procedures (SOPs)

The client's quality control unit will prepare appropriate written validation SOPs that clearly establish which operations need to be documented, what information the documents will contain, how critical information will be verified, who is responsible for generating the documentation, and what approvals are required for each document. SOPs will be written for the process as well as for the use and testing of Computer-related Systems. Qualifications Protocols will be developed, test data reviewed, and summary Qualification Reports written according to written procedures which will assure that validation objectives are met.

The meaning and significance of each approval signature will be defined in writing.

The following are some of the validation activities which would be supported by the clients Standard Operating Procedures (SOPs) and / or guidelines as appropriate (also see 3.8.3.1):

- Process Validation
- Computerized System Qualification
- Preparation of a Validation Project Plan
- Manufacturing Data Specification
- System Requirements Specification
- Supplier Evaluation and Report
- Functional Requirements Specification
- Preparation of a Project and Quality Plan
- Qualification Protocol Preparation
- Qualification Protocol Implementation
- Qualification reporting
- Configuration Management
- Document Management
- GMP Compliance & Project Risk Assessment
- Change Control
- System Access Security (physical and electronic)
- System Operation and Management
- System Training
- Data Backup, Storage and Retrieval
- Contingency Planning and Disaster Recovery
- Periodic Review
- System Maintenance
- Calibration

Siemens does not routinely participate in the preparation of Client driven Validation SOPs, but if required, Siemens as SI may assist in the preparation of selected validation related SOPs. To undertake Pharmaceutical projects, Siemens have available in-house procedures that support the client's validation activities and procedures.

3.0 VALIDATION METHODOLOGY

3.1 Validation Planning (continued):

3.1.4 Project Validation Team

The Project Validation Team is a group of selected management and non-management personnel that will be responsible for the development, review, and approval of all validation-related documents and the supervision of the implementation of the qualification testing. The team would normally reflect the higher level site validation organization and include representation from Quality Management, Information Technology, Engineering and the Owner Department. A specific Validation Team should be identified by job function and included in the Project Validation Plan. In addition, during the course of a validation program, additional individuals may be called on to participate. Non-management personnel should be considered an essential part of the Project Validation Team since these individuals will most likely implement validation-related activities.

Siemens as SI should expect to participate as an integral member of the Validation Team. However, Siemens responsibilities as a member of the team should be clearly defined at project kick-off.

3.0 VALIDATION METHODOLOGY

3.1 Validation Planning (continued):

3.1.5 Validation Project Plan

The Validation Project Plan (also see APPENDIX NO. 1B) is derived from the Validation Master Plan and needs to be closely linked to the Project and Quality Plan.

The purpose of a Validation Project Plan is to provide detailed analysis and definition of the validation documentation and activities that are needed for successful project validation, and also to present a view of the resource planning and management to accomplish this. The plan will identify the processes to be performed or controlled, the systems to be used and should include a GMP compliance and risk analysis. The plan will also define the validation methodology, responsibilities and procedures under which system qualification is to be accomplished.

The Validation Project Plan should put forward a reasoned logical case that the completion of the activities defined is sufficient to ensure documented evidence which provides a high degree of assurance that a computerized system will consistently meet its predetermined specifications and quality attributes.

For the benefit of project team members, client management, supplier representatives and regulatory authority inspectors the plan must communicate:

- GMP Compliance and Risk issues; to enable these findings to be reviewed and confirmed or otherwise at the end of each major validation step.
- Overall philosophy, intention and approach to establishing the performance adequacy of the computerized system.
- Overview of the project and the reasons for the validation activities.
- Responsibilities of the project and validation teams.
- Scope of the validation activities.

The procedures described in a Validation Project Plan should be consistent with established policies and reference the appropriate Validation SOPs. While it is clear that the client's quality management unit has primary responsibility for all specifications and procedures affecting the identity, strength, quality, and purity of the drug products produced in a facility, an important purpose of a Validation Project Plan is to establish:

- specific requirements for system qualification responsibilities
- expectations for each validation task.
- define project deliverables and acceptance criteria
- outline document schedule and milestones

3.0 VALIDATION METHODOLOGY

3.1 Validation Planning

3.1.5 Validation Project Plan (continued):

The specific validation approach described in a Validation Project Plan can be influenced by the complexity of the Computerized System. Qualification of complex computerized systems may require the division of the computerized system into sub-systems, each of which can then be qualified separately (once the sub-systems of a complex computerized system have been qualified, the qualification of the integrated system will be a more reasonable task). Validation Project Plans may be written for a single computerized system or for an entire facility.

Siemens as SI does not routinely participate in the preparation of Validation Project Plans for its client. However, if requested, Siemens may contribute to the development of a client's Validation Project Plan by preparing those sections of the document which pertain to Siemens contracted services. This as a value-added service for regulated clients.

Project and Quality Plan

Quality planning issues need to be addressed to compliment the computerized system planning activities, and this is best achieved with a Project and Quality Plan. Such a plan provides the method by which quality is built into a process control system project.

A comprehensive and accurate Project and Quality Plan is essential so that all staff involved in the project - pharmaceutical manufacturer, supplier or third party - can access a formal definition of project standards, schedule, organization and responsibilities.

The purpose of the Project and Quality Plan is to clearly define how the project is to be controlled and which quality standards are to be applied, and it must communicate this information to all client project team members, supplier representatives or third parties as appropriate.

As the plan will probably be revised during the project it is advisable to structure it in such a way that it can easily be updated.

It is normal for a client's Project and Quality Plan to contain the following sections, and be structured as below:

- Introduction
- Documentation Control
- Project Overview and Scope
- Organization
  - Quality System
  - Structure
  - Responsibilities

3.0 VALIDATION METHODOLOGY

3.1 Validation Planning

3.1.5 Validation Project Plan (continued):

- Implementation Plan
  - Project phases
  - Task schedule
  - Progress control

- Quality Standards and Objectives
- Methods and Tools
- Appendices
  - Detailed Project Plan
  - Approval matrix
  - Project and Quality Plan Activity Schedule

The scope of each section and level of detail required depends on the size and complexity of the project.

The Project and Quality Plan is a formal document produced by the pharmaceutical manufacturer. Issue and revision of the Project and Quality Plan should be controlled by means of an approval matrix, identifying the name, signature and initials of each resource and the general actions they are authorized to carry out. This matrix should also be kept as an appendix of the plan for easy update.

The selected supplier will be expected to produce a Quality Plan for their internal use. This Quality Plan must be in alignment with the client's project and Quality Plan and be agreed with the client.

3.0 VALIDATION METHODOLOGY

3.1 Validation Planning (continued):

3.1.6 Plan Execution

Execution of the Validation Project Plan will afford control and documentation of the validation, and entails conducting all system qualification activities, compilation of the qualification documentation, and recording / reviewing implementation. Achieving this is very much dependent on the suppliers validation knowledge and system qualification methods.

Siemens as SI would normally be contracted for conducting the system development, testing and implementation based on the defined User Requirement Specifications (ex. Definition Phase), through to an approved Installation and Operational Qualification. Siemens project execution procedures and system application knowledge are key attributes for meeting these responsibilities and delivering the appropriate level of validation support documentation for the relevant project phases. On the occasion when Siemens are required to participate in other phase activities, e.g. Front-end Study, Performance Qualification and Maintenance Contracts, Siemens Life-cycle methodology and project procedures will enable Siemens to assist with these tasks within a recognized validation framework.

3.0 VALIDATION METHODOLOGY

3.1 Validation Planning (continued):

3.1.7 GMP Compliance / Project Risk Analysis

There is increasing use of formal GMP compliance and validation project risk analysis on new applications within the pharmaceutical industry. This is seen as a support activity / document for validation planning as it identifies the level of criticality of the computerized system within the manufacturing environment, and determines the risk of not complying with regulatory requirements. The findings of the assessment can be used to adjudge the focus of inspection by regulatory authorities. Such analysis can be complimented during definition and design by application Hazard and Operability Studies. The risk analysis findings should be considered as a key part of the Validation Project Plan , and should be reviewed on completion of each validation step (see Figure 2) to determine whether any activities have / could influence the validation program.

Specifically the implementation of this level of risk management is intended to:

- Give direction and decision support to the implementation groups.
- Provide base information and prioritization for the validation project plan.
- Give the means to identify and assess technical and organizational risk factors that threaten the success of the validation project.
- Identify other more specific areas of the application that would benefit from more detailed risk assessment and / or reduction.
- Provide responses to risks and fall-back plans and identifies any risks in them.
- Place the ownership of risks with those best placed to manage them, and have the necessary expertise, resources and authority to carry out any mitigating action.

This is a relatively new and more focused examination of both the In-Project Related Risk and the Post-Project Residual Risk categories. The former being a risk that the project will not meet anticipated business benefits within acceptable time and cost constraints. The latter being a risk that one of the project outcomes will be the introduction of a new hazard into the regulated operations. A number of techniques exist to assist in identifying and analyzing risks. These include Failure Mode, Effects and Critical Analysis (FMEA), Fault Tree Analysis (FTA). Hazard Analysis and Critical Control Point / Hazard and Operability Study (HAQCCP/HAZOP), any other qualitative and quantitative methods.

The degree of examination that is undertaken in this initial assessment of computerized system criticality and the risk to GMP varies, but at minimum it needs to determine the areas of the application that present a risk (high, medium, low) and the key issues causing this e.g. introducing new technology, introducing a new process stage.

The process of validation described in Siemens Validation Support Manual is suitable for reducing medium residual risks to an acceptable level, i.e. as low as reasonably practicable. In general computer systems used in pharmaceutical manufacture, and that need to be validated, fall into this medium risk category.

At this early stage, Siemens would not routinely participate in analyzing the risk to GMP of system application and operation. However Siemens knowledge of regulatory requirements and how their system(s) functionality aligns with GMP can provide key information and direction for the pharmaceutical manufacturer throughout the computerized system design, construct , integrate / install and qualification steps.

3.0 VALIDATION METHODOLOGY (continued):

3.2 Requirements Definition

A successful validation project depends on a proper definition of what a system is supposed to do and a clear understanding of the requirements at a level which is independent of specific hardware or software.

Defining the requirements for a computerized system is one of the most important steps in assuring that the component process control system meets the client's expectations. The process control system requirements document set, also referred to as the User Requirement Specification, is the foundation for all subsequent process control system design documents. The URS must identify technology and operational requirements for the application.

3.0 VALIDATION METHODOLOGY

3.2 Requirements Definition (continued):

3.2.1 Functional Requirements

The Functional Requirements defines what the process control system must do and how the process must function to be acceptable for the application, i.e. „what must be accomplished„ and includes desired process parameters, operating modes, process descriptions, security, data display/processing/reporting/archiving/ communication, operator interface, and others.

Siemens does not routinely participate in the preparation of Functional Requirements for its client. However, if a client requested assistance, then Siemens as SI could participate as a value-added service. Usually, the Functional Requirements are prepared prior to the selection of the supplier.

3.0 VALIDATION METHODOLOGY

3.2 Requirements Definition (continued):

3.2.2 System Design Requirements

The System Requirements defines the structure of the process control system and other physical attributes, including what components make up the system, including mechanical / electrical / pneumatic components, and control system components (an outline of a typical System Requirement document can be located in Appendix No. 4A).

Siemens does not routinely participate in the preparation of System Requirements for its client. However, if a client requested assistance, then Siemens as SI could participate as a value-added service. Usually, the System Requirements are prepared prior to the selection of the supplier.

3.0 VALIDATION METHODOLOGY

3.2 Requirements Definition (continued):

3.2.3 User Requirement Specification (URS)

The User Requirement Specification, containing the Functional Requirements and the System Requirements of the process control system is the base document from which the selected supplier will prepare a Functional Design Specification. (Combining the Functional Requirement and the System Requirement into a single User Requirement document is normal practice when complex and large systems and processes are to be implemented.)

The URS (also see APPENDIX NO. 4B) is a document written by , or on behalf of, the client. The purpose of the URS is to:

- Provide sufficient detail to the supplier to produce a cost, resource and time estimate to engineer and document the process control system.
- Provide input information required for the system Functional Design Specification (FDS)
- Provide an unambiguous and commonly understood Operational and Interface listings of functional and system requirements, which can be tested during Performance Qualification.
- Include or reference all Manufacturing Data, including Critical Data for system design and testing.

Producing a URS is also a method of ensuring that each internal group within the pharmaceutical manufacturing environment which will be affected by the proposed system is aware of what the new system will, and equally importantly will not, do. It is a way of the pharmaceutical manufacturer arriving at one set of definitive requirements. The level of requirement specification can be independent of specific hardware or software unless the use of specific hardware or software is a requirement.

A URS should not be prepared until the pharmaceutical manufacturer has a full understanding of the requirements. If the requirements are not clear then the instigation of a Front End Study would be the normal course of action.

As a potential supplier Siemens as SI may be requested to assist with a Front End Study and in particular to determine the feasibility of applying a Computerized System, identifying the GMP issues and validation activities that need to be addressed.

A User Requirement Specification should have the following focus:

- Scope Overview
- Project Objectives, including automation philosophy

3.0 VALIDATION METHODOLOGY

3.2 Requirements Definition

3.2.3 User Requirement Specification (URS) (continued):

- Process Description and Operation, including Manufacturing Data (Functional Requirements)
- System Architecture and Functionality (System Requirements)
- Installation and Environmental Requirements
- Project Execution and Life-cycle Services
- Documentation Requirements, including mechanical drawings, electrical diagrams and Process & Instrument Diagrams.
- Defining the requirements for a system requires close teamwork and effective communication among the system users and others involved with its design, implementation, and subsequent maintenance.

In order to provide a systematic approach to defining Computerized Systems, the following five levels of systems are used:

Level 0 : Equipment
Measurement Sensors and control devices that monitor and control the process.

Level 1 : Controller
Control functions or elements that directly adjust final control elements.

Level 2 : Workstation
Operator Consoles (including Graphical User Interface) that allow direct, control and document the process, including manual activities / intervention. Examples of level 2 Process Control Systems are DCS or SCADA systems.

Level 3 : Area
Where other computer-based automation functions are integrated into the process control system (Levels 1 and 2). Examples of a Level 3 Area Computer System include SFC, MHSS, and LIMS Systems.

Level 4 : Factory
Where site level computer-based automation functions are integrated into the Area and Workstation systems. Examples of Level 4 Factory Computerized Systems include MRPII and EBRS Systems.

Through an iterative process involving all members of the Validation Team, the preliminary concept of required functions is refined to identify those features which must be satisfied and those that are desirable. The desired features should be prioritized as to their relative importance. Features that are necessary in order to validate a system should always be considered requirements, not desirable features. How these required functions relate / align with GMP should also be addressed.

3.0 VALIDATION METHODOLOGY

3.2 Requirements Definition

3.2.3 User Requirement Specification (URS) (continued):

Once agreed internally, the URS is issued to prospective suppliers as part of a Request for Quotation (RFQ) for the proposed system. The contractual status of the URS and its importance related to the validation program should be made clear to the supplier. The Supplier must develop the system Functional Design Specification (FDS) from the URS, and for ease of cross reference and verification checks it is advisable to use the same numbering system for the FDS content as for the URS; this providing simple and direct cross reference to corresponding sections and their content. (This document content numbering practice greatly aids document review and can be carried forward to lower level
specifications and the test procedures that need to correspond to each specified requirement).

It is recognized that the Functional Design Specification may supersede the URS as the definitive specification for system design, but the URS remains the definitive technical statement of client requirements and must be maintained up to date throughout the life of the system. The URS also remains the base document against which Performance Qualification (PQ) acceptance is proven.

In summary, producing a computerized system requirements specification in the form of the URS provides the following key benefits for a validation project:

- Clarifies technical, quality and documentation requirements to the Supplier.
- Enables the pharmaceutical manufacturer to assess the technical, regulatory and commercial compliance, or otherwise, of submitted bids against a formal specification.
- Ensures a structured approach to the presentation of information which can be carried forward into the specifications produced during the system development phase.

Siemens does not routinely participate in the preparation of Computerized System Requirements Specification for its client. However, if a client requested assistance or if Siemens was a preferred supplier, then Siemens as SI could undertake application related technology studies as an added value service. Usually, user requirement specifications are prepared prior to the selection of the supplier and included in a formal Request-For-Quotation (RFQ) to which Siemens would respond.

3.0 VALIDATION METHODOLOGY

3.2 Requirements Definition (continued):

3.2.4 Manufacturing Data

Approved an accurate detail of manufacturing / operation is essential for the process control system supplier to fully understand and engineer the Pharmaceutical manufacturer's application. This manufacturing data is an important part of the Computerized System Requirement definition and should be available for inclusion in or reference by the User Requirement Specification.

For a complex or large production / manufacturing process operation the type and level of detail that needs to be presented is considerable. This information is fundamental to control technology / data transfer, and ensures that sufficient and accurate information and criteria is available for developing the automation application. Not surprisingly, this will also provide a key element for qualification of the automation system and via Performance Qualification to validation of the process.

The pharmaceutical manufacturer's aim will be to determine full and accurate requirement data and develop a manufacturing data specification; an approved document that can be used for design, design review and test criteria. This specification should support the compliance and risk analysis and used to identify and include Critical Process Data*:* parameters, limits and data which is essential in determining and ensuring the satisfactory quality of a drug product. It is extremely important that this information is controlled and available in a timely manner so that automation definition, and thereafter design, commissioning and operation proceeds efficiently and in support of GMP and validation requirements.

The manufacturing data should cover all items of measurement and control appropriate to an automation system. and describe:

- Regulatory requirements.
- Product detail and Registration documentation cross-reference.
- Operating procedures.
- All parameters which are to be measured or controlled, including those that could compromise the quality and acceptability of the product (sometimes called *Critical Process Data*).
- All alarms, fail safe actions of control devices, and any hard wired trips and their impact on the process.
- Any special process requirements.
- Materials of construction.

All the process parameters to be measured or controlled will have been determined by the pharmaceutical manufacturer's system Owner Department and Quality Assurance. <u>These parameters / data are not therefore open to interpretation</u>.

Siemens does not routinely participate in the preparation of the manufacturing data element of the Computerized System Requirements for its client. However, if a client requested assistance with identifying data and the level of detail needed to engineer the Process control system then Siemens as SI may provide this value-added service. Usually, requirement specifications are prepared prior to the selection of the supplier and included in a formal Request-For-Quotation (RFQ) to which Siemens would respond.

3.0 VALIDATION METHODOLOGY

3.2 Requirements Definition (continued):

3.2.5 Request for Quotation (RFQ)

The Client's Inquiry package is normally sent out to pre-qualified suppliers, and can take many forms depending on the complexity and size of project. However, the document set needs to provide all the elements necessary for a typical project, plus definition of validation responsibilities and deliverables, ranging from procedures to suitable resource and documentation.

Inquiry packages need to provide a sound basis for system selection and award of contract in support of validation documentation. The use of a formal tendering process provides the pharmaceutical manufacturer with an auditable method of documenting supplier selection.

A documentation matrix should be provided that defines all the documents that should exist in the project validation file.

Key validation documents that should form part of the inquiry package are:

- Project Validation Plan
- Detailed Scope of Work
- Documentation Requirements
- User Requirements Specification
- Manufacturing Data Specification

Potential suppliers will be requested to supply a Project and Quality Plan.

The pharmaceutical manufacturer should request all technical information relevant to the tender in a standard form, and the supplier could be asked to specify their solution by addressing one or more of the following documents:

- User Requirements Specification
- Manufacturing Data Specification
- Supplier Documentation Requirements

It is important to demonstrate the capability to provide a structured, auditable system of documentation which covers all phases of the project and validation life-cycle, and one that can be easily maintained /updated when changes occur. In particular the supplier should organize the documentation into a Project Validation File.

Contracts should only be placed with suppliers of process control systems who can meet all requirements with regards to implementing a validation project.

Siemens does not routinely participate in the preparation of the Request for Quotation exercise and the Inquiry Package for its client. However, Siemens as SI have procedures in place that enable them to identify all key elements, particularly validation document and resource requirements, and ensure a structured response.

3.0 VALIDATION METHODOLOGY

3.2 Requirements Definition (continued):

3.2.6 Requirements Specification Review and Report

The Requirements Specification Review is a technical, quality and commercial review of the Inquiry / requirements package. This is beneficial not only in checking the accuracy of one of the fundamental elements of a prospective validation program, but also before significant resources have been committed to a specific project. Problems found at this point can be more easily resolved, saving time and money, and reducing the likelihood of missing a critical issue.

An important objective of the Requirement Specification Review is to establish an auditable system of documentation which can be easily maintained throughout the computerized system life-cycle, and ensure approved and controlled transition with fully documented record, to the Design Phase.

The pharmaceutical manufacturer should have a procedure to enable requirement review to be conducted in a consistent and thorough manner such as to provide verification of the project definition and requirements specification. A review of the GMP Compliance / Validation Project Risk Assessment should also be undertaken at this time and included as a section in the review report.

The purpose of the review (sometimes called the Requirement Specification Qualification) is to ensure that the project and the computerized system requirements have been adequately defined and the requirements fully specified before issuing the Request for Quotation to prospective suppliers. It is a complete review of all technical, quality and commercial aspects of the Inquiry package. This package may include not only the requirements specification of the Process control system, but that of the measurement and control instrumentation and associated networks and interfaces to other systems.

Following a successful review meeting, a Requirements Review Report and Certificate should be prepared by the pharmaceutical manufacturer and signed by designated members of the validation team. Approved requirements definition is now available for the selected supplier to commence the Design and Construct Phases.

Siemens does not routinely participate in the Requirements Specification review process for its client. However, it is advisable that Siemens as SI are knowledgeable on the issues that determine qualification of the Definition Phase, as on occasions that they are already the pharmaceutical manufacturer's contracted supplier (e.g. through an „alliance„ agreement), it is likely that they will be invited to be on the review team to address both the technical and validation issues in review of the documentation pertaining to a Computerized System development and implementation.

3.0 VALIDATION METHODOLOGY (continued):

3.3 Select Suppliers

Selection of the supplier of a Process control system is based primarily on the ability of the supplier to satisfy the client's Computerized System Requirements. Whether the supplier is an outside company or an internal department, the supply of a system that can be qualified as part of a validation plan is the primary consideration. Selection of the Process control system involves evaluation of the suppliers development and project methods as well as evaluation of the proposed hardware and software. This is normally initiated by undertaking supplier audits with the purpose of identifying those suppliers who are suitably placed to respond to a Request for Quotation.

It is important to understand the different types of audit :

- First party audits (internal audits by the pharmaceutical manufacturer on itself).
- Second party audits (by the pharmaceutical manufacturer or their representatives on its external or internal suppliers)
- Third party audits (of suppliers by an organization acting independently of the pharmaceutical manufacturer; probably on behalf of the supplier).

Furthermore, audits can have different focus:

- Company audits (covering the organization and its Quality Management System).
- Product audits (covering specific products, functionality of the product and maintenance support).
- Method audits (checking the adequacy of the Quality Management System, including support documentation).
- Compliance audits (checking for evidence of compliance with the Quality Management System).

The scope of each audit is defined by the pharmaceutical manufacturer and agreed with the auditor(s) and the supplier during audit planning. The audit process can have four main stages:

1. Pre-Audit Questionnaire (also known as preliminary assessment, initial evaluation, assessment, per-qualification). A questionnaire is used in this process to gather enough information in order to take a broad view on the suitability of prospective suppliers. It is useful in obtaining relevant supplier documents prior to the detailed audit and can at times precede a presentation by the supplier to overview the system, work practices, and experience. This type of preliminary audit provides useful initial information to aid planning of the detailed audit.

2. Pre-contract audit (sometimes called in-depth, full quality, detailed audits). These are the most common audits conducted by pharmaceutical manufacturers, and are normally carried out pre-contract, during validation planning.

3. Follow-up audit (re-audit, development monitoring, corrective action monitoring). These check on issues raised during the detailed audit, or that agreed corrective actions have been implemented.

4. In-contract audit (periodic, surveillance). These are periodic audits planned to verify that the supplier is maintaining the required standards as agreed in contract or as seen during previous audits. They may focus on general issues or on critical project related issues.

3.0 VALIDATION METHODOLOGY

3.3 Select Suppliers (continued):

Siemens recognizes the importance of Supplier Evaluation in the clients validation program, and will support those evaluations fully. Clients will be provided access to any and all relevant quality documents that they request. Given timely notice, Siemens support an evaluation visit by a client or Third Party auditor. But the quality documents remain at Siemens site.

At a minimum, the following areas would normally need be evaluated:

- Management commitment
- Organization Structure
- Financial History and Stability
- Software Development Methodology
- Quality Programs and standards certification
- Project Management methods and SOPs
- Resource availability and qualifications
- Document Management
- Change Control
- Review and Approval Process
- Internal Audits
- System life planning and migration
- Component Development Records
- Configuration Management
- Expertise in pharmaceutical applications
- System functionality to support GMP / Validation
- Maintenance support, procedures, including service equipment
- System Documentation
- Test Record Archive
- Contingency Plans and Disaster Recovery Strategy
- Personnel training program
- Professional Affiliations
- Confidentiality

For computerized system the following Software Quality Assurance (SQA) practices / procedures are important to the pharmaceutical manufacturer:

- Programming Standards
- Programming tools
- Structural testing practices
- System practices documentation
- Software / Hardware Design practices
- Data Integrity testing documentation
- Database testing documentation

3.0 VALIDATION METHODOLOGY

3.3 Select Suppliers (continued):

- Functional testing documentation
- Version control
- Deviation Analysis and Corrective Action Records
- Access Security
- Back-up
- Virus Detection
- Client Problem Reporting / Solving / Fault Notification

For each stage, but in particular the Pre-contract Audit an Audit Report will be produced. The audit report is important in that it serves as the formal record of the audit and its findings, and is a major input when determining corrective action.

The audit report is intended to present an accurate, objective record of a computer system supplier's operations, and will include key documentation gathered during the audit.

An audit report will normally contain:

- an introduction
- scope information
- organization of audit, including agenda / schedule, criteria, representatives
- detailed findings
- record of closing meeting
- analysis and conclusions

Some clients will also require that the audit report includes specific recommendations by the audit team.

Audit reports are retained as part of the overall validation documentation for the Computerized System and are normally treated as confidential.

On receiving the audit report, the client has a number of options on how to progress selection of the process control system supplier:

- To use the supplier unconditionally.
- To use the supplier for certain components only (possibly version specific)
- To use the supplier subject to completion of specific corrective actions.
- To agree to a documented Quality System with the supplier for the purposes of the contract.
- To prohibit the use of the supplier.

If the supplier is requested to carry out corrective actions as the result of an audit, then the pharmaceutical manufacturer will normally follow these up and obtain documentary evidence of successful completion. Evidence could include copies of new procedures, testing records, design and code review documents. A letter of confirmation from the supplier is not normally sufficient.

3.0 VALIDATION METHODOLOGY

3.3 Select Suppliers (continued):

(In general the inspection process is similar to that which the pharmaceutical manufacturer has to accommodate from the Regulatory Authorities, but the exception and privilege of a previously agreed agenda.)

A suitable and prospective supplier will be technically competent and commercially qualified to supply and support the proposed system. Knowledge of validation requirements and experience in providing systems for GMP-regulated applications are important selection criteria.

Quotation assessment and the resulting contract award is normally dependent on a similar criteria addressed in the audits, i.e. technical, validation and project methodology, application experience, and commercial conditions and value.

Siemens understands the process and objectives of supplier evaluation and selection, and will plan to have trained personnel to host the client's audit team. Siemens intention will be to facilitate a prepared environment, with timely and accurate response to the audit requirements as they unfold. Siemens does not routinely participate in the audit team for audits of computerized system suppliers, but as required, Siemens would conduct similar audits of sub-system suppliers and / or associated system integrators and engineering contractors. Siemens will adopt procedures that enable them to effectively accommodate and conduct such audits.

3.0 VALIDATION METHODOLOGY

3.3 Select Suppliers (continued):

3.3.1 Methods Evaluation

Quality System

The pharmaceutical manufacturer will be looking for the existence of a structured quality system that demonstrates a method of assuring quality in component and services offered. The quality system will need to be documented (policy manual, procedures, standards etc.), with evidence that it is consistently in use.

They will seek verification of the maturity of the Quality Management System with regard to the component / service being audited, and examine control of documentation with regard to reviews, approvals, distribution and update.

Certification to a recognized standard (e.g. ISO 9001) is desirable, but not essential, provided the Quality System is prepared and controlled to the same level.

They will expect to see deviation, change control and review reports on the use and results of the Quality system.

The Quality System will be evaluated on how it is organized and conducted against the basic processes required for software development, maintenance and support. The following will be examined:

Framework Processes
- Managing the Organization
- Roles and responsibilities
- Quality assurance reporting chain
- Defining , maintaining and improving the quality system
- Conducting internal quality system audits

Life-cycle processes
- Reviewing contracts, tenders and orders
- Defining requirements
- Development planning
- Quality planning
- Design and implementation
- Review, testing and qualification
- Acceptance
- Replication, delivery and installation
- Maintenance

3.0 VALIDATION METHODOLOGY

3.3 Select Suppliers

3.3.1 Methods Evaluation (continued):

Supporting Processes

- Configuration management
- Controlling documents and data
- Controlling quality records, including Failure Rate tracking.
- Measurement
- Controlling rules, practices and conventions
- Root Cause Analysis
- Corrective Action program
- Client notification
- Controlling tools and techniques
- Purchasing
- Controlling other included software components
- Independent reviews
- Training

3.0 VALIDATION METHODOLOGY

3.3 Select Suppliers

3.3.1 Methods Evaluation (continued):

3.3.1.1 Project Methodology

Siemens life-cycle project methodology is based on conducting each project phase activity to the Phase Model described in Section 3.1.1. A typical activity „input / output„ chart for the Software / Hardware Integration stage is illustrated in Table 1 below.

Table 1

Input Documents	Phase Description/Tasks	Output Documents Software Configuration
Overall and detailed specifications, design information Use of standards (e.g. regulations, unit operation...), typicals	Automation system configuration: : CFCs, SFCs, phases / control modules ...	Software documentation with "SW wiring of the Tags", CFC, SFC plans, parameter lists of control modules, operational modes of phases, parameter lists of phases / operations, recipes ...
	Configure/program operator stations: process / plant diagrams, messages, measurement curves ..., links to the automation systems, call-back routines	Development documentation with lists of configured objects: process diagrams, messages, curves, including the SW connection to the automation system.
	Configure host computer (generate recipes and unit operations, set up phases ...)	Development documentation with recipes, unit operations, control parameters ...
	Specify the HW/SW configuration required to perform the tests. Specify test cases for the configuration data	Test document for configured SW
	Review and release of the test document	Review report, release report of the test document for config. SW
	Perform the SW test with simulated process peripherals	Test report for configured SW
	Release of the tests	SW Release report

3.0 VALIDATION METHODOLOGY

3.3 Select Suppliers

3.3.1 Methods Evaluation

3.3.1.2 Project Methodology (continued):

The pharmaceutical manufacturer will be seeking evidence of a documented process for planning, conducting, controlling, tracking, reviewing and reporting all project activities and costs in a structured and consistent manner throughout all project and validation phases.

The project management system must deal with not only controlled input / output, but with the communication strategy, specification traceability, changes, deviations and program / resource management.

How compilation and verification of an up-to-date Project Validation File is achieved will be very much in focus.

3.0 VALIDATION METHODOLOGY

3.3 Select Suppliers

3.3.1 Methods Evaluation (continued):

3.3.1.2 Supplier Quality Plan

A Quality Plan (see APPENDIX NO. 6) will be produced by Siemens as the first deliverable during the Design Phase.

A preliminary quality plan may also be requested during the supplier selection exercise for information and assessment as to how the prospective supplier identifies and addresses the quality issues related to a computerized system validation project. The Supplier Quality Plan must define actions, deliverables, responsibilities and procedures to satisfy the high level Project and Quality Plan which is produced by the pharmaceutical manufacturer during the Project Planning and Definition Phases. As such it would be expected to include detail of the supplier's Software Quality Assurance Plan (SQAP).

The purpose of the Supplier Quality Plan is to clearly define how the project is to be controlled and which quality standards are to be applied, and it must communicate this information to all client project team members, supplier representatives or third parties as appropriate.

The Supplier Quality Plan may be revised at various points in the project. Such revision should be approved by both the supplier and the client and be subject to change control.

3.0 VALIDATION METHODOLOGY

3.3 Select Suppliers (continued):

3.3.2 Component Evaluation

3.3.2.1 Software

If software is being developed for the application, the supplier's Software Quality Assurance program would be a major factor in indicating the ability of the supplier to provide an acceptable process control system.

For new systems the development and testing methods and documentation record of the operating system software, would probably be examined to the same level as application specific software development methodology (see Appendix No. 11A, for reference to an Evaluation Report on Siemens Development and Application Practices).

Software Quality Assurance is a defined and systematic set of activities necessary to provide adequate confidence that a software item or component conforms to predefined specifications.

The requirements and issues covered in Section 3.3.1.1, Quality System will be applicable for operating system software evaluation and configured application specific software development methodology.

Software development should include a review and checking process for evaluating the components of a given development phase to ensure correctness and consistency with respect to the components and standards provided as input to that phase. In addition, there should be test plans and the corresponding test records to demonstrate compliance with specified requirements. The entire development process should be carried out under written and approved procedures and all design, testing and verification activities documented, reviewed and approved.

Source Code availability and accessibility are also important requirements for the pharmaceutical manufacturer in meeting validation requirements; this for application software and the operating system.

Data integrity within the system and associated networks / interfaces need to be examined. For this the process control system supplier should be able to demonstrate recognized standard data communication protocols and on-board diagnostics that conduct, monitor, and record accurate data transfer throughout the system.

Siemens is responsible for instituting and conforming to a Quality System that ensures quality assurance for software development, testing and implementation for the Process Control System. The approach enables this vital validation activity to provide well structured and documented software that can be maintained throughout the life of the computerized system. Siemens conducts their software development and testing procedures in line with the life-cycle and phase models described in 3.1.1. See also 1.3.5 Table 1 and Appendix 11.

3.0 VALIDATION METHODOLOGY

3.3 Select Suppliers

3.3.2 Component Evaluation

3.3.2.1 Software (continued):

Evaluation and selection criteria for the software depends upon the type of software being evaluated. For standard programs such as an operating system or a canned configurable program, the history of satisfactory use is of major importance. The number of installations, particularly GMP-related applications, and the length of time the current version of the program has been in use, in conjunction with a review of relevant software problem reports and the history of changes to the program, can provide convincing evidence that a program is structurally sound. If software is being modified or developed for the application, primary emphasis should be placed on evaluating the vendor's software development program plan and associated procedures.

Five (5) categories of software are recognized (see descriptions in Section 3.5.1) and include, Operating System Software, User Programmable Firmware , Standard (Canned) Software, Configurable Software, and Custom Built (Bespoke) Software. These classifications are not considered to be rigid, but they allow important distinctions to be made regarding supplier software testing.

The purpose of software testing is to provide a high degree of assurance that the system using the software operates in accordance with the system specifications. Testing of software to be used in a computerized system should include both structural verification and functional testing. For validation purposes, software testing can be classified as being either Structural Verification or Functional Testing. If sufficient documented evidence can be provided to support the assertion that software is structurally sound, it is not necessary for the client to perform Structural Verification to assure proper operation. The client can verify the documented evidence through a Supplier audit. However, Functional Testing of software is always required in the qualification of a Computerized System.

Structural Verification

Structural verification of software is the detailed examination of the functional logic of code to verify that it conforms to software requirements and specifications. It also includes the inspection of the program for adherence to development standards and procedures. Structural verification may include specific activities such as branch testing, path testing and statement testing. Source code in a human readable form is required to perform Structural Verification. Structural verification can be conducted effectively during software development. This is particularly true of configurable software. It is also important to have other program documentation such as logic diagrams, description of modules, definition of all variables, and specifications of all inputs and outputs.

Siemens is responsible for providing test procedures and performing Structural Testing of the program code that it develops, and for maintaining documented records of the tests. (see Appendix No. 11A, for reference to an Evaluation Report on Siemens Development and Application Practices).

3.0 VALIDATION METHODOLOGY

3.3 Select Suppliers

3.3.2 Component Evaluation

3.3.2.1 Software (continued):

Functional Testing

Functional Testing of software evaluates outputs of a program compared with the expected output values for a range of input values and other specified parameters. Functional Testing may be performed using simulated inputs to the software or by testing the computerized system. Functional Testing of software does not require access to the source code, but it does require a comprehensive system specification describing all functions of the system in sufficient detail to define the tests required to assure that the system will operate in the intended manner. While source code may not be required for Functional Testing, it may be very helpful; and complete and accurate descriptions of all functional routines such as calculation algorithms and control strategies should be available to the client. As in the case of Structural Verification, it is important to have program documentation such as logic diagrams, descriptions of modules, definitions of all variables, and specifications of all inputs and outputs.

Siemens is responsible for the performance of Functional Testing of the program code that it develops and for maintaining documented records of the tests. (see Appendix No. 11A, for reference to an Evaluation Report on Siemens Development and Application Practices)

It is normal for configurable software components to perform three (3) types of software testing, namely:
- Module Testing
- Integration Testing
- System Testing

The first two tests are performed as part of the development effort. The module testing uses a „white box„ (sometimes referred to as „glass„ or „clear„ box) approach. This testing is performed with full knowledge of how the module was programmed. The integration testing uses a „gray box„ approach where modules have been assembled together. This testing is performed with an understanding of the software architecture, but is not designed to stress each function of each module.

The „black box„ testing is the final functional system test. This testing is performed from a client perspective where no detailed knowledge of the module design or software architecture is required or expected. The first two types of tests provide „structural„ verification of the software. The final testing being used to ensure that the functional system requirements have been met. This test „model„ using the three types of testing means each of these tests provides a different level of assurance. Functional testing cannot confirm the structural integrity of software modules, nor can structural testing confirm that a system will meet the functional requirements.

Siemens is responsible for providing test procedures and for the performing all software module, integration and system test levels, documenting their adherence to the test procedures by test record analysis and approval. This includes system integration (i.e. Siemens software / hardware, critical data interfaces to other systems), and debugging activities (see Appendix No. 11A, for reference to an Evaluation Report on Siemens Development and Application Practices).

3.0 VALIDATION METHODOLOGY

3.3 Select Suppliers

3.3.2 Component Evaluation (continued):

3.3.2.2 Hardware Evaluation

Hardware evaluation tends to be less complex than software evaluation. The system will be developed utilizing the same life-cycle approach as the software, and unless hardware is being designed and built specifically for the application, will generally be composed of standard modules with performance specifications that can be evaluated relative to the Functional Requirements and operational specifications.

There will be focus on the history of equipment use in similar applications; availability of replacement parts and service for the expected lifetime of the system; durability, reliability, repeatability, and accuracy commensurate with the application. The evaluation will also examine the ease of field calibration, self documentation, and availability of adequate standards. Other areas which will be scrutinized regarding reliability and accuracy include:

- Conformance of the sub-systems to their specifications in terms of :
  - Memory
  - Peripherals
  - Processing Units
  - Storage
  - Housing
  - Sub-systems interconnections such as cables, connectors, and junction boxes.

- Conformance of sub-system and external interfaces to their specifications in terms of :
  - Timing
  - Noise rejection
  - Voltage and Current protection
  - Polarity
  - Intrinsic safety
  - Isolation
  - Alignment of channels
  - EMC regulations
  - RFI regulations
  - Analogue range, limits, conversion accuracy and resolution, sampling rate
  - Digital timing and validity conditions
  - Pulse conversion factors and update rate
  - Interface protocols and conformance to transmission distance, connector and cabling requirements.

- Tolerance to expected physical/environmental conditions including :
  - Transmission distances
  - Operating temperature, humidity and pressure
  - Chemical contact
  - Vibration

3.0 VALIDATION METHODOLOGY

3.3 Select Suppliers

3.3.2 Component Evaluation

3.3.2.2 Hardware Evaluation (continued):

- Conformance of electrical supply in terms of :
  - Filtering
  - Loading
  - Earthing
  - Failure and interrupts

- Safety and Security features :
  - Defined safe state on failure
  - Action of equipment to supply interruptions of different time periods (milliseconds, seconds, minutes, hours)
  - Hardware alarms and interlocks
  - Redundancy
  - Graceful degradation
  - Fault tolerance
  - Watchdogs
  - Automatic integrity checks

- All modes of operation, e.g.
  - Start up
  - Shutdown
  - Testing/Maintenance

- Manufacturers test diagnostic routines for :
  - CPU
  - Memory (all types)
  - Distributed processors
  - Peripherals

The Quality processes and procedures need to be applied as stringently to hardware as to software, so that validation support documentation for system development, application, testing, operation and maintenance are accurate, auditable and current.

Siemens is responsible for providing test procedures, performing Functional Testing of the hardware that it develops, and documenting the results. This includes system integration, networks and all necessary debugging activities (see Appendix No. 11A, for reference to an Evaluation Report on Siemens Development and Application Practices).

3.0 VALIDATION METHODOLOGY

3.3 Select Suppliers

3.3.2 Component Evaluation

3.3.2.2 Hardware Evaluation (continued):

Software / Component Release

Software / Component Release procedures and authority will receive attention to ensure components are suitable for client use. It is advisable to have release authority with a test group who are independent of the development team.

Only upon the successful completion of the software / component testing and documentation review should component release be authorized. Once a software program is released, it should be placed under formal Change Control and any revisions must follow the requirements of the Change Control procedure.

Siemens is responsible for software / system release and is able to provide auditable documentation to show the satisfactory development and testing of the system.

3.0 VALIDATION METHODOLOGY

3.3 Select Suppliers (continued):

3.3.3 Supplier Evaluation and Report

This section overviews the typical project activities that the client has to undertake to report, review and decide on suppliers' proposals.

Resolving Queries

Any queries about the Inquiry package should be submitted in writing and all replies also communicated in writing. All original queries, and subsequent replies, should be kept in the pharmaceutical manufacturer's project validation file.

All queries and replies to queries, should be sent to all prospective suppliers to ensure all issues are known to each prospective supplier. This is particularly important if clarification on validation issues are involved.

Where a major problem is encountered, it may be necessary to re-issue the tender package to each supplier. The closing date may then need to be reviewed. All documentation relating to such an event should be maintained in the pharmaceutical manufacturer's project validation file.

Receipt of Quotations

On receipt of each submission the client should ensure that written acknowledgment is issued to the supplier itemizing all documentation received.

Review of Quotations

The purpose of the quotation review process is to select the best proposal.

The client should have arranged the make-up of the quotation review team and should organize a review meeting on or after the closing date. The team should include all necessary disciplines to ensure quality, validation, manufacturing, technical, commercial and safety requirements are properly addressed .

An initial independent evaluation of each tender should be undertaken to ensure that each tender complies with the Inquiry package and can be compared like for like. Any points requiring clarification should be noted. The review process could take several meetings depending on the complexity and size of the system involved. Each review meeting should be formally recorded.

After the initial evaluation suppliers could be asked to clarify their submissions.

The conclusion of any clarification discussion should be recorded and could lead to revised submissions. All such records should be retained in the pharmaceutical manufacturer's project validation file.

3.0 VALIDATION METHODOLOGY

3.3 Select Suppliers

3.3.3 Supplier Evaluation and Report (continued):

Once each quotation has been clarified the final review and evaluation can commence. The quotation should be evaluated methodically against the following criteria:

- capability of supplier to meet all project and support requirements.
- compliance of proposed system with URS.
- costs of proposed system.

The tender analysis process and results/decisions should be formally documented and a copy maintained in the project validation file.

At this stage in the evaluation the one or two most favored suppliers should be visited and audited.

Unsolicited revisions from individual suppliers after the closing date are normally rejected and the incident recorded.

Supplier Audits

Following the tender review, and if no recent audits have been undertaken, the most favorable one or two suppliers should be visited and an audit of technical, quality and validation procedures undertaken as necessary.

The audit will be undertaken as described in Section 3.3 and will cover:

- Corporate overview and resources
- Quality system and certification
- Purchasing (including control of suppliers)
- Project management
- Systems engineering
- Production/manufacturing
- Software design and development
- Testing (Hardware, Software, Integration / Acceptance)
- Delivery and installation
- Hand-over and final documentation
- Calibration
- Support/maintenance
- Documentation management
- Change control
- Software configuration management

All observations should be agreed with the supplier and an audit report produced, including those observations, and also conclusions and recommendations. The audit reports should be maintained in the project validation file and used as input into the final selection process.

3.0 VALIDATION METHODOLOGY

3.3 Select Suppliers

3.3.3 Supplier Evaluation and Report (continued):

Supplier Selection

At the end of the review process the pharmaceutical manufacturer or his representative should produce a report which summarizes the compliance and key benefits of each system, the costs, delivery dates and program.

The results of the final evaluation / selection stage should be documented along with the major findings of the audit report. A review of the GMP Compliance / Validation Project Risk Analysis should undertaken at this time and included as a section in the audit report. This information should form the basis for the recommendation of the preferred supplier. The recommendation should be made in the report, and the reasons for the final decision should be stated.

This report should be submitted for approval by management along with all the necessary supporting documentation. All relevant documentation should be retained in the project validation file.

Siemens recognizes the need to be technically competent and commercially qualified to supply and support computerized systems. Siemens have a planned development process, appropriate quality assurance, work procedures and documentation to support pharmaceutical applications. Siemens knowledge of validation requirements and experience in providing systems for GMP-regulated applications are considered value-added attributes and important selection criteria.

Award of Contract

Changes which have been agreed between the pharmaceutical manufacturer and the selected supplier should be made to the tender Inquiry documents and the submitted quotation / tender.

A formal agreement should then be prepared by the pharmaceutical manufacturer, which references the relevant documents. This agreement should be signed by the Client and Supplier representatives who are authorized to do so. A purchase order is also raised which references the final agreement and other relevant documentation. A copy of the signed final agreement and purchase order should be retained in the pharmaceutical manufacturer's project validation file. The selected supplier should be reminded of the confidentiality agreement (which should be extended as necessary on award of contract).

Unsuccessful Tenders

After the contract award, each unsuccessful supplier should be informed in writing that they have not been chosen. Each unsuccessful supplier should also be reminded of the confidentiality agreement binding on them in relation to information supplied. All material issued to suppliers during the Inquiry period should be returned.

An important objective of Selection Review is to support an auditable system of documentation which can be easily maintained throughout the computerized system life-cycle.

3.0 VALIDATION METHODOLOGY (continued):

3.4 Design Computerized System

As with other components of the computerized system, adherence to the life-cycle development methodology will enable a Process Control System to be designed, tested and documented in accordance with the User Requirements Specification and in line with the Project Validation Plan.
The life-cycle methodology ensures a structured approach to process control system design and imposes rigorous testing and documentation review requirements at all stages.

Siemens standard components (e.g. SIMATIC PCS 7) are designed (developed, tested, produced, documented, etc.) in accordance to the life cycle model described herein. A mapping of this generic life cycle model to the current practice within Siemens as Standard Component Supplier is shown in Table 1. The compliance of Siemens internal procedures with this life cycle model is summarized in Appendix 11A. The following clauses are written specifically for the System Integrator, but similar processes must be used by standard component suppliers.

General Requirements

All design and implementation revision and modifications must be progressed through an agreed documentation management system operating under a strict change control procedure.

For the computerized system the overall design will be based on three (3) documents: the Functional Design Specification, the associated system Acceptance Test Specification, and the Quality Plan.

The system integrator shall produce a quality plan for the project which details the agreed approach to quality throughout the project life cycle (also see Section 3.3.1.3 and 3.1.6).

The system integration and factory acceptance test specifications, including network testing are also produced by the supplier based on the Functional Design Specification (see Sections 3.5.6 and 3.5.7).

Computerized system specification cannot be completed until the supplier(s) and the specific hardware, software, and controlled equipment to be used have been selected.

It is recognized that the system integrator is most knowledgeable about how the process control system operates, and the client must provide appropriate specifications of the Controlled Functions and the Operating Environment.

It is anticipated that changes to the computerized system specifications will be required based on information gained during the development, testing, installation, and qualification of the system. Once the computerized system design specification has been approved and placed in a state of control, all changes should be made according to SOPs which assure that all related documents such as program listings, operator manuals, Qualification Protocols, and installation drawings are modified to reflect the changes and that training requirements are updated as appropriate.

3.0 VALIDATION METHODOLOGY

3.4 Design Computerized System (continued):

3.4.1 Functional Design Specification (FDS)

The Functional Design Specification (FDS) is the cornerstone of the IQ and OQ qualification phases of a process control system. It is a high level document that is written by the supplier and describes clearly and completely how the intended process control system will meet the client's application needs as set out in the URS. As such it should be produced and formatted so that the requirements detailed in the User Requirements Specification (URS), can be easily identified (i.e. traceable back to source) and audited. It is not unusual for the FDS to be developed jointly by the supplier and the client: this, particularly when the application is large and complex.

The FDS is the basis for development of the Qualification Protocols and should identify all measurable or determinable parameters which may affect system performance and include the acceptable values or characteristics of each critical parameter. A critical parameter being one which will affect the state-of-control of the computerized system if it deviates from an acceptable range of values.

The FDS should contain all of the information required to describe how the system will operate in all of its normal operating modes and how it will respond to abnormal conditions. It is important that detailed information on the interfaces between the Computerized System, Operating Environment is included. In doing so, it may refer to other documents such as construction drawings, equipment manuals, or SOPs for more detailed information.

The Functional Design Specification is normally both a contractual document and a key validation document, and as such, must be approved for use by both Siemens as SI and the pharmaceutical manufacturer.

Once the Functional Design Specification is produced there will be a formal verification that it addresses properly all the functions of the User Requirement Specification that are to be implemented by the system.

When the Functional Design specification is approved it is possible to generate a System Integration and Acceptance Test Specification. It is advantageous to produce these documents in parallel so that the functions defined are testable.

The Functional Design Specification should define:

- The functions to be performed by the system.
- The system networks, particularly connections to the manufacturing process via measurement and control instrumentation.
- The system interfaces, particularly interfaces to other systems.
- The manufacturing data on which the system will operate.
- Testing and diagnostic provisions.
- All non-functional considerations, such as:
  - quality requirements
  - regulatory and documentation requirements
  - operators of the system

3.0 VALIDATION METHODOLOGY

3.4 Design Computerized System

3.4.1 Functional Design Specification (continued):

- reliability
- hardware
- performance
- compatibility with other systems
- maintenance
- adaptability
- ease of training
- ease of operation
- security, including data integrity and disaster recovery
- physical environment
- cost and time scale considerations

As the Functional Design Specification is to define how the system is to meet the requirements defined in the User Requirements Specification, any divergence between the FDS and the URS should be clearly identified by the supplier and documented, giving reasons for the difference. Any divergence to be reviewed and approved by the pharmaceutical manufacturer.

As a contractual document, approved by both Siemens and the client, the FDS, if so required by the pharmaceutical manufacturer may contractually supersede the URS. It is therefore important that the client checks the FDS for conformance with the requirements stated in the URS.

Any non-conformance, due for example to time constraints or costs, should be resolved between Siemens and client prior to approval. Any technical non-compliance must be fully documented as a supplement or update to the URS. This is very important as the FDS is normally the base document for the System Integration Tests, and also Factory and Site Acceptance Tests (FAT and SAT).

Omissions and misinterpretations, if not detected at this stage, will inevitably lead to the need for later modifications, with the possibility of project delays, budgetary overruns. These could impact the project validation program and consequently overall project milestones.

Once the FDS is approved, it must be kept under formal change control by Siemens as SI to cover any subsequent amendments. Change control should also be applied to any dependent documents.

In summary, the Functional Design Specification has the following key objectives:

- Defines how the supplier's system will meet the needs of the pharmaceutical manufacturer as detailed in the URS. This will be achieved by the supplier stating what the system will do, how it will be used, and its attributes (i.e. the FDS is the physical mapping of the supplier's system onto the URS).

3.0 VALIDATION METHODOLOGY

3.4 Design Computerized System

3.4.1 Functional Design Specification (continued):

- Enables the client to determine the feasibility of the manner in which the supplier will meet the requirements stated in the URS.
- Allows the client to understand the extent to which the system, as defined, meets the requirements of the URS.
- Ensures a structured approach to the presentation of information which can be carried forward into the design and test specifications produced later in the system development.

(The considerations for, and structure of a typical computerized system Functional Design Specification can be seen in APPENDIX NO. 7B and APPENDIX 7A.)

Siemens routinely participates in the preparation of computerized system Functional Design Specifications for its clients. Siemens addresses the client requirements (previously documented by the client) and prepare the Functional Design Specification . Siemens‘ project approach to modular system design is described in Section 3.1.1and Section 3.3.1.2.

3.0 VALIDATION METHODOLOGY

3.4 Design Computerized System (continued):

3.4.2 Hardware Design Specification

The Hardware Design Specification (HDS) is a document written by the supplier. It details how the supplier intends to provide system hardware to implement the aims set out in the Functional Design Specification (FDS). The HDS is a description of computer hardware equipment to be supplied and how it is to be connected to any other computer or plant equipment. The HDS should describe in more detail the system hardware and other equipment identified in the FDS and as such should provide traceability back to statements in the FDS which can be audited (an audit trail).

Once the Hardware Design Specification is produced and approved it is possible to generate a Hardware Test Specification. It is advantageous to produce these documents in parallel so that the hardware definition and test correspond.

The computer hardware production should follow the requirements stated in the Hardware Design Specification.

Hardware should where possible be produced using standard units / components from recognized and audited suppliers (like Siemens), who can offer suitable maintenance procedures.

The HDS has two main uses:
- For use by the supplier as a working document during the design and development of the system.
- For use after qualification of the system as support documentation by those responsible for the maintenance and future enhancement of the system hardware.

For these reasons the HDS defines:
- Overall system hardware design
- Individual hardware components that together constitute the system
- Intercommunication links between items of system hardware
- Intercommunication links between the system hardware and external systems
- Hardware performance
- Engineering and Assembly Standards

Other hardware design considerations, such as:
- environment
- safety
- service requirements
- enhancements
- security

3.0 VALIDATION METHODOLOGY

3.4 Design Computerized System

3.4.2 Hardware Design Specification (continued):

As the HDS will define in detail the system hardware, any divergence between the HDS and the FDS should be clearly identified by the supplier. Any divergence should be reviewed between the pharmaceutical manufacturer and the supplier, and the outcome reflected in controlled changes to the FDS and / or HDS to ensure consistency.

The HDS is not normally a contractual document, but should still be understandable by the pharmaceutical manufacturer and Regulatory Authorities. The client should review their role with regard to this document in light of the experience available to them. It may not be appropriate to approve the HDS, but may be appropriate to provide comment on its content. However, any non-conformance to the FDS should be resolved between the supplier and the pharmaceutical manufacturer at this stage.

Once the HDS is supplied, the client should ensure that there is an agreed procedure for identifying and notifying any discrepancies that arise between the HDS and the FDS. This to ensure that an acceptable revision of requirements can be achieved and appropriate changes made to the FDS and HDS.

Many different techniques and methodologies are available to the supplier for use in the HDS, these should be appropriate to the type of system being implemented and agreed with the client. In addition to the use of text and natural language descriptions, the document may include:

- Block diagrams
- Wiring diagrams
- Network diagrams
- Data flow diagrams

In summary, the HDS has the following key objectives :

- Defines the constituent hardware components of the system, how they inter-communicate and what constraints are applied to them.
- Defines any communication to external systems and associated hardware requirements.
- Enables the client to determine the implementation strategy of the supplier.
- Enables the supplier to demonstrate the correctness and completeness of the hardware design with the FDS.
- Allows the client to understand the hardware design and cross-check with the FDS.
- Provides input to the hardware test specification.

The structure of the HDS should be similar to that of the FDS to facilitate the cross checking of the two documents. A cross reference should be included in the HDS indicating the degree of compliance with the FDS. This cross reference may be included as an appendix to the HDS.

The HDS should be structured in a way that will permit easy access to information. A means of referencing items such as chapters, lists, tables and figures may be necessary.

3.0 VALIDATION METHODOLOGY

3.4 Design Computerized System

3.4.2 Hardware Design Specification (continued):

A number of general guidelines apply:

- Vague or ambiguous statements should be avoided. The scope for readers to make assumptions or misinterpret should be minimized.
- Each sub-system and any interfaces between sub-systems should have unique references.
- The interfaces between sub-systems should be testable.

Whenever connections to measurement and control instrumentation are to be utilized, the HDS should fully define the instruments in a manner consistent with the instrument application data.

A suggested structure for the HDS is as follows:

1. Introduction

2. System Overview

3. Detailed Hardware Design
   - Sub-system Specifications
   - Sub-system Integration
   - System Interfaces

4. Other Design Information
   - System Environment
   - Assembly Specifications
   - Electrical Supplies
   - Modes of Operation
   - Availability (including built-redundancy levels)
   - Safety
   - Security and Data Integrity
   - Compatibility and Enhancement Potential
   - Maintainability
   - Delivery and Installation

5. Terminology

   The above structure ensures that all major topics are covered by the HDS. However it is recognized that the HDS author needs to structure the information in a manner most appropriate to the system in question.

3.0 VALIDATION METHODOLOGY

3.4 Design Computerized System (continued):

3.4.3 Software Design Specification

It is recognized that for GMP-critical software development must be based on a fully documented, reviewed and structured design, following good programming practices to ensure it is:

- reliable
- safe
- robust
- maintainable
- testable
- modular in structure
- well laid out
- well commented

The Software Design Specification (SDS) is written by Siemens as SI and is a description of the application software to be provided as part of the system. The SDS should describe in more detail the system software described in the FDS and as such should provide traceability back to statements in the FDS which can be audited (an audit trail).

Once the Software Design Specification is produced and approved it is possible to generate a Software Module Integration Test Specification. It is advantageous to produce these documents in parallel so that the software definition and test correspond.

The SDS details the manner in which Siemens under a Software Quality Assurance Plan, intends to provide system software to implement the aims set out in the FDS. It has two distinct uses that should be borne in mind during the production of the document :

- It is used by the supplier as a working document during the design and development of the system, to ensure efficient and effective software development.

- It is used after qualification of the system as support documentation by those responsible for the maintenance and future enhancement of the system. As such it should provide enough information to make the software system intelligible.

For these reasons the SDS defines:

- The overall system structure.
- The subsystems that constitute the system.
- The interfaces between the subsystems.
- The performance expected of the system.
- The data on which the system will operate.
- All non-functional considerations, such as:

3.0 VALIDATION METHODOLOGY

3.4 Design Computerized System

3.4.3 Software Design Specification (continued):

- operators of the system
- safety
- hardware
- adaptability
- security

As the SDS will define how the system software will meet the aims defined in the FDS, it is essential to include cross-references to specific clauses in the FDS. It is also essential that any divergence between the SDS and the FDS should be clearly identified by the supplier. The divergence should be reviewed by the pharmaceutical manufacturer and the supplier, and the outcome reflected in controlled changes to the FDS and SDS to ensure consistency.

The SDS is not normally a contractual document, but should still be understandable by the client and regulatory authorities. The client should review their role with regard to this document in light of the experience available to them. It may not be appropriate to approve the SDS, but may be appropriate to provide comment on its content. However, any non-conformance to the FDS should be resolved between Siemens and the client at this stage.

Omissions and misinterpretations, if not detected at this stage, will inevitably lead to the need for later modifications, with the possibility of project delays and budgetary overruns.

Once the SDS is supplied, the client should ensure that there is an agreed procedure for identifying and notifying any discrepancies that arise between the SDS and the FDS, such that an acceptable revision of requirements can be achieved and appropriate changes made to the FDS and SDS.

Many different techniques and methodologies are available to the supplier which may be used in the SDS, as appropriate to the type of system being implemented. In addition to the use of text and natural language descriptions, the document may include such things as:

- Formal language descriptions and design methodology
- Structure diagrams
- Data flow diagrams
- Decision Tables
- Database descriptions where appropriate, such as entity relationship models

It should be noted that some form of diagrammatic representation of the system should always be provided as they are essential in understanding the structure and flows through the system.

In summary, the Software Design Specification has the following key objectives :

3.0 VALIDATION METHODOLOGY

3.4 Design Computerized System

3.4.3 Software Design Specification (continued):

- Define the constituent software components of the system, how they inter-communicate and what constraints are applied to them.
- Enables the client to determine the implementation strategy of the supplier.
- Allows the client to ensure the correctness and completeness of the software design through cross-checking with the FDS.
- Provides input to the system integration test specification.
- Ensures a structured approach to the presentation of information which can be carried forward into the module design and test specifications produced later in the system development.

The structure of the SDS should be similar to that of the FDS to facilitate the cross checking of the two documents. A cross reference should be included in the SDS indicating the degree of compliance with the FDS. This cross reference may be included as an appendix to the SDS.

The SDS should be structured in a way that will permit easy access to information. A means of referencing items such as chapters, lists, tables and figures is necessary, particularly since the Software Design Specification is to be cross-referenced to the System Integration Module Test Specification.

A number of general guidelines apply:

- Vague or ambiguous statements should be avoided. The scope for readers to make assumptions or misinterpret should be minimized.
- Each module and any interfaces between modules should have unique references.
- The interfaces between modules should be testable. This is particularly important for systems subject to validation because the integration testing performed by the supplier is carried out against the SDS.

A suggested structure for the SDS is as follows:

1. Introduction

2. System overview
   - Logical module structure
   - Mapping between logical modules and physical implementation
   - Methodologies employed, and rationale for structure
   - Relationships between modules

3.0 VALIDATION METHODOLOGY

3.4 Design Computerized System

3.4.3 Software Design Specification (continued):

3. Development documentation

4. Good Software Production Practice

5. Module descriptions
   - Operation
   - Interfaces between modules
   - Performance
   - Alarm handling
   - Error handling
   - Event handling
   - Data
   - Data integrity
   - Security
   - System safety
   - Hardware configuration
   - Software configuration

6. Module Interfaces
   - Equipment (Plant/System)
   - Other Systems
   - Operators

7. Terminology

   The above structure ensures that all major topics are covered by the SDS. However it is recognized that the SDS author needs the ability to structure the information in a manner most appropriate to the system in question.

Software Module Design Specification

For each software sub-system (module) identified in the Software Design Specification, a Software Module Design Specification (SMDS) shall be available or produced. The SMDS is a document written by Siemens as SI and details the manner in which Siemens intends to provide and apply a software module that implements the module's design as set out in the SDS. The Software Module Design Specification should contain enough information to enable coding of the module to proceed. Each Software Design Module should provide traceability back to statements in the SDS which can be audited (an audit trail).

3.0 VALIDATION METHODOLOGY

3.4 Design Computerized System

3.4.3 Software Design Specification (continued):

Once the Software Module Design Specification is produced and approved it is possible to generate a Software Module Test Specification. It is advantageous to produce these documents in parallel so that the software definition and test correspond.

The Software Module Design Specification has two distinct uses that should be borne in mind during the production of the document:

- It is used by the supplier as a working document during the coding of the module, to ensure the correctness and completeness of the code.

- It is used after qualification of the system as support documentation by those responsible for the maintenance and future enhancement of the system. As such it should provide enough information to make the module intelligible.

For these reasons the SMDS defines:
- The module functions.
- The module inputs and outputs.
- Details of interlocks.
- Detailed logic and structure of the code.
- Internal data formats.
- Intermediate communication within the module.
- The interfaces to other systems or modules.

As the SMDS will define how the proposed system will implement the appropriate modules design defined in the SDS, any divergence between the SMDS and the specific module described in the SDS should be clearly identified by the supplier, and the outcome reflected in controlled changes to the FDS and SDS to ensure consistency.

The SMDS is not normally a contractual document, but should still be understandable by the client and regulatory authorities. The client should review their role with regard to this document in light of the experience available to them. It may not be appropriate to approve the SMDS, but may be appropriate to provide comment on its content. However, any non-conformance to the SDS should be resolved between the supplier and the client at this stage.

Once the SMDS is supplied, the client and Siemens as SI should ensure that there is an agreed procedure for identifying and notifying any discrepancies that arise between the SMDS and the SDS, such that an acceptable revision of requirements can be achieved and appropriate changes made to the SDS and SMDS under a strict change control procedure.

3.0 VALIDATION METHODOLOGY

3.4 Design Computerized System

3.4.3 Software Design Specification (continued):

Many different techniques and methodologies are available to the supplier, and these should be appropriate to the type of system being implemented and agreed with the client. In addition to the use of text and natural language descriptions, the document may include such things as:

- Pseudo code
- Control Flow diagrams, Logic Flow diagrams, State Transition diagrams, Sequential Flow Charts
- Decision Tables
- Database descriptions where appropriate, such as entity relationship models

It should be noted that some form of diagrammatic representation of the system should always be provided as they are essential in understanding the structure and flows through the system.

In summary, the Software Module Design Specification has the following key objectives :

- Define the implementation of individual modules, how they communicate with the complete system and what constraints are applied to them.

- Enables the client to determine the implementation strategy of the supplier.

- Allows the client to ensure the correctness and completeness of the software implementation through cross-checking with the SDS.

- Provides input to the Software Module Test Specifications.

- Ensures a structured approach to the presentation of information which can be carried forward into the software module test specifications.

The structure of the SMDS should be similar to that of the SDS to facilitate the cross checking of the two documents. A cross reference should be included in the SMDS indicating the degree of compliance with the SDS. This cross reference may be included as an appendix to the SMDS.

The SMDS should be structured in a way that will permit easy access to information. A means of referencing items such as chapters, lists, tables and figures is necessary, particularly since the Software Module Design Specification is to be cross-referenced to its associated Software Module Test Specification.

A number of general guidelines apply:

- Vague or ambiguous statements should be avoided. The scope for readers to make assumptions or to misinterpret should be minimized.

- Each module and any interfaces to other modules or systems should have unique references.

3.0 VALIDATION METHODOLOGY

3.4 Design Computerized System

3.4.3 Software Design Specification (continued):

- The module functions should be testable. This is particularly important for systems subject to validation because the module tests performed by the supplier are carried out against the corresponding SMDS.

A suggested structure for the SMDS is as follows:

1. Introduction

2. Overview
   - Module Design
   - Design Constraints

3. Documentation

4. Good Software Production Practice

5. Module Description
   - Function
   - Initiation
   - Inputs and Outputs
   - Interlocks
   - Detailed logic and structure
   - Performance
   - Alarm Handling
   - Error handling
   - Event Handling
   - Security

6. Module Data
   - Internal Data
   - System Data

7. Module Interfaces
   - Equipment (Plant/System)
   - Other Modules
   - Global Data, Semaphores, Flags, Events
   - Common Procedures, Sequences, Sub-sequences

8. SMDS/SDS Cross reference

9. Terminology

3.0 VALIDATION METHODOLOGY

3.4 Design Computerized System

3.4.3 Software Design Specification (continued):

The above structure ensures that all major topics are covered by the SMDS. However it is recognized that the SMDS author needs the ability to structure the information in a manner most appropriate to the system in question.

Siemens as SI routinely participate in the preparation of all lower level software and hardware design specifications for its clients. These system design specifications are derived from the Functional Design Specification previously prepared by Siemens.

Instrumentation Application Design

However the design of Measurement and control Instrumentation should be based around an established, integrated, documentation system which enables additions and changes to be properly implemented and audited. The contents of a typical integrated documentation system which is widely used in the pharmaceutical industry is listed below:

- Drawing Register
- Instrument Schedule
- Instrument Purchasing Specifications/Data Sheets
- Instrument loop Schematics
- Logic diagrams and Control Schematics
- Instrument Location Drawings
- Instrument Installation Details
- Panel Layout Drawings
- Panel Piping and Wiring Diagrams
- Control Room Layout Drawings
- Cable / Tubing Routing
- Junction Box Layouts
- Cable / Tubing Schedules
- Installation Material Summary
- Instrument Installation Specification

This being a guide to the level of documentation that is expected to be provided for and as the result of design.

Depending on the extent of contract services Siemens as SI may provide the measurement and control instrumentation. In such a case Siemens would participate in the preparation of all instrument application engineering and specification activities and documentation. This would be carried out under Siemens project engineering procedures .

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System

In the Construct period the development and testing of the process control system is performed at several levels.

Siemens as SI will normally be responsible for all levels of system development and testing, with client involvement as necessary for the validation program and as agreed under the contract. The client may not wish to attend all of the low level system tests (e.g. software module tests, hardware tests etc.), but will normally attend and witness the Factory Acceptance Test prior to delivery to site. The supplier and the pharmaceutical manufacturer should jointly approve the FAT test results and test report.

All levels of testing must be fully documented to include test specifications and the results of testing in the form of signed off written test sheets, and reports.

In general development test plans should include the following points:

- description of the test environment, indicating type and version of software and hardware and / or test equipment
- identification of test personnel
- identification of verification / approval personnel

The proposed tests should identify the following :

- Test objectives, describing what must be examined and should be derived from the appropriate system specification.
- Test cases providing detailed descriptions of the test objective and should be such that test specifications can be derived directly from them.
- A Test Specification that describes the test conditions necessary for the tests to be executed.
- The expected result or acceptance criteria representing the data or conditions that must be achieved.

The description of the test execution should clearly describe the actions which lead to the test results. The type of record maintained must indicate how the test execution and test results are documented.

For the purposes of test evaluation the documented test results are compared with the expected results or acceptance criteria. The tests are considered complete once it has been confirmed that the acceptance criteria have been sufficiently met and all documentation is such as to enable the entire test procedure to be reproduced by a third party with the requisite knowledge.

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System (continued):

3.5.1 Software Types

It is recognized that software commonly found in computerized systems can be grouped into five (5) types. These categories can then be used as a basis for determining an appropriate validation approach.

The fitness for purpose of any proposed solution should be assessed, and any history of usage in similar applications considered when determining the category.

The categories listed below help in developing a validation strategy. However, the potential effects of a system failure must also be considered in the assessment.

Category 1: Operating Systems

Standard, commercially available operating systems that are used in pharmaceutical production are considered validated when they are used in projects where the application software that runs on this platform is included in the validation process - i.e. the operating system itself is not directly validated, rather, it is validated as a part of the application that runs on it. This does not preclude auditing activities related to software development of the operating system. Reputable operating systems must be used, and the operating system's name and version must be recorded in the equipment IQ. New versions should be reviewed prior to use and consideration given to the impact of new, amended, or removed features on the application. Findings from this review could lead to a formal re-testing program of the application, particularly where a major upgrade of the operating system has occurred.

Category 2: Standard Instruments, Micro-Controllers, Intelligent Transmitters / Devices

These are driven by non user programmable firmware. Examples of these are weighing systems, bar-code scanners, PID controllers etc. They are configurable, and the configuration must be recorded in the equipment IQ. The unintended and undocumented introduction of new versions of firmware during maintenance must be avoided through strict maintenance procedures and change control. The impact of new versions on the validity of the IQ documentation should be reviewed and appropriate action taken.

Depending on the number of worldwide installations and its perceived value, it should be decided whether a validation should be performed for the equipment/firmware. In any case, its interaction with the components of the process control system must be validated.

Category 3: Standard Software Packages (e.g. Excel, Lotus 1-2-3)

These are widely known as Canned or COTS (Commercial-Off-The-Shelf) configurable packages. There is no requirement to validate these software packages, but the use of new versions should be reviewed and subject to stringent change control. Validation effort should concentrate on the application, which includes:

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System

3.5.1 Software Types (continued):

- system requirements and functionality
- the high level language or macros used to build the application
- critical algorithms and parameters
- data integrity, accuracy and reliability
- operational procedures

Category 4: Configurable Software

These are referred to as "custom configurable packages". Examples of these are Process Control Systems (PCS), Supervisory Control and Data Acquisition Systems (SCADA), MES, LIMS and MRP packages.

The system and platform should be well known and proven before being considered in Category 4, otherwise Category 5 should apply. These systems permit clients to develop their own application by configuring / amending predefined software modules and also developing new application software modules. Each application (of the standard component) is therefore specific to the pharmaceutical manufacturing process and maintenance is a key issue, particularly when new versions of the standard component are produced.

A recognized validation methodology must be used to implement the application and particular attention should be paid to any additional or amended code and to the configuration of the standard modules. A software review of the modified code should be undertaken and documented to an approved procedure.

In addition, an audit of the supplier is required in order to determine the level of quality and structural testing built into the standard component. The audit needs to consider the development of the standard component and examine the procedures and documentation that control the development process.

Based on the results of the audit and the complexity of the application, the validation plan should document exactly which measures are required to validate an application.

Category 5: Custom Built or Bespoke Systems

This is software that has been specially written for a client application. There are instances of this type of system in the pharmaceutical industry, and the full validation life-cycle must be applied to all parts of the system.

An audit of the supplier is required to examine their quality systems and a validation plan should be prepared to document precisely what activities are necessary, based on the findings of the audit and the complexity of the proposed system.

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System

3.5.1 Software Types (continued):

Table 2 below shows the validation approach for the software types previously outlined:

Table 2: Validation Methods

Category	Validation Methods
1	Record the version
2	Record the configuration
3	Validate the application
4	Audit Supplier, validate the application and any client specific code
5	Audit Supplier, validate the complete system

It should be noted that complex systems often have layers of software, and one system could exhibit several or even all of the software categories described above.

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System (continued):

3.5.2 Software Module Test Specification

For each Software Module Design Specification, an associated Software Module Test Specification (SMTS) shall be produced by the supplier. The Software Module tests to be carried out shall ensure that the software module meets its specification.

Each test should be clear and unambiguous, written without the use of jargon, should clearly state the what constitutes a pass and a failure, and should be traceable back to statements in the appropriate Software Module Design Specification which can be audited (an audit trail).

Test reports shall be produced and approved by Siemens as SI and also by the client if required under the contract.

The SMTS is primarily for the supplier's own use, and describes all tests to be performed on a module to fully test the module and its interfacing to any external devices. It defines:

- A brief outline of the module to be tested.
- The tests to be performed upon the module.
- The data on which the tests will be performed.
- The expected results from the tests.
- The personnel who will carry out and witness the tests.
- The environment and location in which the tests are to take place.
- The equipment on which the tests are to take place.
- The test equipment needed.
- The test documentation required.

It should be noted that there is likely to be more than one software module within any system, and therefore there will be more than one software module test specification.

The objective of producing a SMTS is to demonstrate that the supplied module correctly implements its functionality, as defined in the SMDS, in a controlled and repeatable manner.

The SMTS should ideally be prepared by a person who has knowledge of the appropriate SMDS but who has not been involved in its implementation. This is to ensure that the testing is not influenced by knowledge of the individual module.

The SMTS should not attempt to exhaustively test all module functions, input, outputs, errors, alarms, and performance variables. The purpose of the document is to test as wide and representative a cross section as possible.

The basis and extent of testing to prove adherence to all specified limits must be documented, clearly identifying the reasons for the decisions made, in order to provide reassurance that Siemens has adequately tested the software module.

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System

3.5.2 Software Module Test Specification (continued):

All test equipment or test software required should be explicitly stated in the SMTS.

Testing against the SMTS should be carried out as many times as necessary to achieve an acceptable level of confidence in the consistant functioning of each module. Siemens will not proceed with Software Module Integration Testing until they are confident with the results of the individual Software Module Tests.

It is in the interest of Siemens that problems are minimized at this stage. (Faults at this stage are unlikely to cause a major problem provided they are rectified prior to Software Module Integration Testing).

The SMTS should address the following areas:

- Initiation
  - Check module start up.
  - Restart of module after failure.
  - Shutdown.

- Program flow control
  - Module activity is correctly controlled.
  - Test correct implementation of algorithms.

- Interrupt or state driven systems activated on the occurrence of specific events, e.g. External Calls, Interrupts, Real-time clocks. Their action and side effects may be tested against the following:
  - Method of initiation.
  - Scheduling.
  - Timed entry.
  - Default actions when sequences fail.
  - Response of signal to erroneous messages with checks for recovery procedures.
  - Batch operations.

- Alarm Handling
  - Check enable/disable
  - Check display
  - Check priorities
  - Check acknowledgment
  - Check recording
  - Check storage and capacity prior to overwriting
  - Check archiving
  - Check overriding

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System

3.5.2 Software Module Test Specification (continued):

- Error Handling
  - Check enable/disable
  - Check display
  - Check priorities
  - Check acknowledgment
  - Check recording
  - Check storage and capacity prior to overwriting
  - Check archiving
  - Check overriding
  - Check recovery from errors

- Event handling
  - Check enable/disable
  - Check storage and capacity prior to overwriting
  - Check archiving

- Report generation
  - Check content
  - Check format
  - Check archiving of data sources

- Operator interfaces
  - Check data validation/verification
  - Check formats
  - Check consistency

- Data input, output and associated protocols.
  - Data types passed between sub-systems.
  - Protocols used in receipt or transmission of data.
  - Data shared between sub-systems.

The testers can make use of protocol or line analyzers to identify signals sent and provide test software or equipment to simulate the returned signals.

- Module security aspects
  - Checking access restrictions.
  - Checking data recovery procedures.
  - Checking logging and archiving of data.

- Module Interfaces
  - Equipment Interfaces
  - Interfaces to other modules
  - Use of system data, semaphores, flags, and events

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System

3.5.2 Software Module Test Specification (continued):

An individual SMTS can contain a large number of tests. It should therefore be structured in a way that will permit easy referencing to the module functionality specified in its associated SMDS.

A number of general guidelines apply:

- The functions and attributes specified in the SMDS should be covered to a sufficient depth to ensure confidence in the module.
- It is the responsibility of the suppliers' project team to determine the extent of these tests.
- Each test action should be defined precisely, the tester should always be clear of the action to take and what constitutes a test pass. Vague statements or criteria should be avoided.
- Each test script should have a unique test reference
- Test scripts should not be duplicated.
- The test scripts should be logically ordered e.g. in the same order as the module functions and attributes described in the SMDS, and this ordering method should be clearly explained.
- The clients will not normally be involved in the testing against the SMTS, however the client may request that they witness these tests.

A suggested structure for the SMTS is as follows:

1. Introduction
2. Scope
3. Test Scripts
4. Test Requirements
   - Test Personnel
   - Reference Documents
   - Test Data
   - Test Equipment
5. SMDS/SMTS Cross References
6. Terminology

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System (continued):

3.5.3 Software Module Integration Test Specification

The Software Module Integration Test Specification (SMITS) is written and carried out by Siemens as SI and details those tests which demonstrate that all software modules communicate with each other correctly and that the software system meets the requirements of the Software Design Specification. A Software Module Integration Test Specification should be written when more than one software module has been produced.

Each test should be clear and unambiguous, written without the use of jargon, should clearly state the what constitutes a pass and a failure, and should be traceable back to statements in the Software Design Specification which can be audited (an audit trail).

Test reports shall be produced and approved by Siemens and also the client if required under the contract.

The SMITS is a document is primarily for Siemens own use, and describes all tests to be performed on the supplied system to fully test the integration between the software modules and also to any external devices. It defines:

- A brief outline of the modules to be tested.
- The tests to be performed upon the interfaces between modules.
- The data on which the tests will be performed.
- The expected results from the tests.
- The personnel who will carry out and witness the tests.
- The environment and location in which the tests are to take place.
- The equipment on which the tests are to take place.
- The test equipment needed.
- The test documentation required.

The objective of producing a SMITS is to demonstrate that the modules in the supplied system, correctly interact with each other and with external software and equipment, as specified in the SDS.

The SMITS should ideally be prepared by a person who has knowledge of the SDS but who has not been involved in the implementation, this is to ensure that the testing is not influenced by knowledge of the system.

The SMITS should not attempt to exhaustively test all interactions between all modules, the purpose of the document is to test as wide and representative a cross section as possible.

The basis and extent of testing to prove adherence to all specified limits must be documented, clearly identifying the reasons for the decisions made, in order to provide reassurance that the supplier has adequately tested the integrated software modules.

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System

3.5.3 Software Module Integration Test Specification (continued):

All test equipment or test software required should be explicitly stated in the SMITS.

Testing against the SMITS should be carried out as many times as necessary to achieve this goal to be satisfied with the level of testing performed. Siemens will not proceed with System Integration Testing or Factory Acceptance Testing until they are confident with the results of the Software Module Integration Testing.

It is in the interest of Siemens that problems are minimized at this stage. (Faults at this stage are unlikely to lead to a loss of confidence in the supplier by the pharmaceutical manufacturer, provided they are rectified prior to Acceptance Testing.)

Prior to providing the resources required to undertake System Acceptance Testing, the client may request Siemens for copies of the test results and test documents to satisfy themselves that the supplier has performed adequate testing and followed agreed quality procedures.

The SMITS should address the following areas:

- Initiation, restart and recovery
  - Check modules started.
  - Restart of system after failure.
  - Shutdown.

- Program flow control
  - Module scheduling and activity is correctly controlled.
  - Test correct running between modules.

- Communications between modules.
  - Modes of access.
  - Communications protocols.
  - Channel capacity.
  - Performance and safety related features.

- Interrupt or state driven systems activated on the occurrence of specific events, e.g. External Calls, Interrupts, Real-time clocks. Their action and side effects may be tested against the following:
  - Method of initiation.
  - Scheduling.
  - Timed entry.
  - Default actions when sequences fail.
  - Response of signal to erroneous messages with checks for recovery procedures.
  - Batch operations.

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System

3.5.3 Software Module Integration Test Specification (continued):

- Alarm handling
  - Check enable/disable
  - Check display
  - Check priorities
  - Check acknowledgment
  - Check recording
  - Check storage and capacity prior to overwriting
  - Check archiving
  - Check overriding

- Error handling
  - Check enable/disable
  - Check display
  - Check priorities
  - Check acknowledgment
  - Check recording
  - Check storage and capacity prior to overwriting
  - Check archiving
  - Check overriding
  - Check recovery from errors

- Event handling
  - Check enable/disable
  - Check storage and capacity prior to overwriting
  - Check archiving

- Report generation
  - Check content
  - Check format
  - Check archiving of data sources

- Operator interfaces
  - Check data validation/verification
  - Check formats
  - Check consistency

- Data input, output and associated protocols.
  - Data types passed between modules.
  - Protocols used in receipt or transmission of data.
  - Data shared between modules.

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System

3.5.3 Software Module Integration Test Specification (continued):

The testers can make use of protocol or line analyzers to identify signals sent and provide test software or equipment to simulate the returned signals.

- Integrity
  - Test that processes share system resources in a predicable and safe manner.
  - Check that the modules have no unwanted side-effects.

- Module security aspects
  - Checking access restrictions.
  - Checking data recovery procedures.
  - Checking logging and archiving of data.

The SMITS can contain a large number of tests. It should therefore be structured in a way that will permit easy referencing to the module interfaces specified in the *SDS*.

A number of general guidelines apply:

- The module interfaces specified in the SDS should be covered to a sufficient depth to ensure confidence in the system.

- It is the responsibility of the suppliers' project team to determine the extent of these tests.

- Each test action should be defined precisely, the tester should always be clear of the action to take and what constitutes a test pass. Vague statements or criteria should be avoided.

- Each test script should have a unique test reference

- Test scripts should not be duplicated.

- The Test scripts should be logically ordered e.g. in the same order as the modules described in the SDS, and this ordering method should be clearly explained.

- The pharmaceutical manufacturer will not normally be involved in the testing against the SMITS, however the client may request that they witness these tests.

A suggested structure for the SMITS is as follows:

1. Introduction

2. Scope

3. Test Scripts

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System

3.5.3 Software Module Integration Test Specification (continued):

4. Test Requirements
   - Test Personnel
   - Reference Documents
   - Test Data
   - Test Equipment

5. SDS/SMITS Cross References

6. Terminology

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System (continued):

3.5.4 Hardware Test Specification

The Hardware Test Specification (HTS) is written and conducted by Siemens, and details those tests to be carried out on the hardware described in the Hardware Design Specification. These tests shall ensure that the system hardware and equipment to be supplied meets its specification and integrates correctly with any existing system hardware or plant equipment.

Each test should be clear and unambiguous, written without the use of jargon, should clearly state the what constitutes a pass and a failure, and should be traceable back to statements in the HDS which can be audited (an audit trail).

Test reports shall be produced and approved by Siemens and also the pharmaceutical manufacturer if required under the contract.

The Hardware Test Specification defines:

- The equipment on which the tests are to take place.
- The assembly checks to be carried out.
- The tests to be performed upon the hardware.
- The inputs on which the tests will be performed.
- The expected results from the tests.
- The personnel who will carry out and witness the tests.
- The environment and location in which the tests are to take place.
- The test equipment needed.
- The test documentation required..

The objective of producing an HTS is so that the supplier tests their chosen hardware against a formal specification to ensure that it meets the requirements defined in the Hardware Design Specification and Functional Design Specification.

The HTS is ideally prepared by a person who has knowledge of the HDS but who has not been involved in its implementation. This is to ensure that the testing is not influenced by knowledge of the hardware.

The basis and extent of testing to prove adherence to all specified limits must be documented, clearly identifying the reasons for the decisions made, in order to provide reassurance that Siemens has adequately tested the hardware.

All test equipment or test software required should be explicitly stated in the HTS.

Conditions which are to be satisfied prior to start of testing should be stated in the test plan.

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System

3.5.4 Hardware Test Specification (continued):

The HTS should include tests covering the following:

- Conformance of the sub-systems to their specifications in terms of :
  - Memory
  - Peripherals
  - Processing Units
  - Storage
  - Housing
  - Sub-systems interconnections such as cables, connectors, and junction boxes.

- Conformance of sub-system and external interfaces to their specifications in terms of :
  - Timing
  - Noise rejection
  - Voltage and Current protection
  - Polarity
  - Intrinsic safety
  - Isolation
  - Alignment of channels
  - EMC regulations
  - RFI regulations
  - Analogue range, limits, conversion accuracy and resolution, sampling rate
  - Digital timing and validity conditions
  - Pulse conversion factors and update rate
  - Interface protocols and conformance to transmission distance, connector and cabling requirements.

- Tolerance to expected physical/environmental conditions including :
  - Transmission distances
  - Operating temperature, humidity and pressure
  - Chemical contact
  - Vibration

- Conformance of electrical supply in terms of :
  - Filtering
  - Loading
  - Earthing
  - Failure and interrupts

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System

3.5.4 Hardware Test Specification (continued):

- Safety and Security features :
  - Defined safe state on failure
  - Action of equipment to supply interruptions of different time periods (milliseconds, seconds, minutes, hours)
  - Hardware alarms and interlocks
  - Redundancy
  - Graceful degradation
  - Fault tolerance
  - Watchdogs
  - Automatic integrity checks

- All modes of operation, e.g.
  - Start up
  - Shutdown
  - Testing/Maintenance

- Manufacturers test diagnostic routines for :
  - CPU
  - Memory (all types)
  - Distributed processors
  - Peripherals

The HTS can contain a large number of tests. It should therefore be structured in a way that will permit easy referencing to the hardware design elements specified in the HDS.

A number of general guidelines apply:

- Each sub-system and interface specified in the HDS should be covered by at least one test in the HTS.

- It is the responsibility of the suppliers' project team to determine the extent of these tests.

- Each test action should be defined precisely, the tester should always be clear on the action to take and what constitutes a test pass. Vague statements or criteria should be avoided.

- Each test script should have a unique test reference

- Test scripts should not be duplicated.

- The Test scripts should be logically ordered e.g. in the same order as the sub-systems and interfaces in the HDS, and this ordering method should be clearly explained.

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System

3.5.4 Hardware Test Specification (continued):

- The pharmaceutical manufacturer will not normally be involved in the testing against the HDS, however the client may request that they witness these tests.

A suggested structure for the HTS is as follows:

1. Introduction

2. Scope

3. Test Scripts

4. Test Requirements
   - Test Personnel
   - Reference Documents
   - Test Data
   - Test Equipment

5. HDS Cross References

6. Terminology

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System (continued):

3.5.5 System Build

Once the Computer-related System Specification has been jointly approved, the Computer-related System is constructed including the following activities:

- Requisitioning of system components such as hardware, software, and any associated instrumentation that is part of the contracted supply
- Application software / Program development
- Hardwiring of Components
- Various Assembly Activities
- Documentation Preparation

Based on the jointly-approved system specification(s), Siemens constructs / develops the computerized system. During construction, Siemens maintains close contact with the client to assure that the client's needs and expectations are met or exceeded.

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System (continued):

3.5.6 System Integration Test Specification

The System Integration Test Specification is written by Siemens as SI and is a description of those tests to be carried out by the supplier prior to the process control system factory acceptance test attended by the client. This to ensure that the tested hardware and integrated software modules operate as intended when integrated to form a complete system.

The specification shall define the testing requirements of the complete system including its database and networks over the whole of its operating range including limits, alarms and boundary testing. The system integration tests will usually include most (or a large proportion) of the factory acceptance tests as well as other areas necessary to ensure the compatibility of the various parts of the system;
hence, could be included as part of the Acceptance Test Specification (see 3.5.7).

System integration testing is an in-house exercise in preparation for the Factory Acceptance Test, and must be documented particularly for deviation and corrective action record. Elements of this testing may be conducted as part of software module acceptance testing. If this is the case the reasons for such an approach and detail of the tests must be recorded.

Each test should be clear and unambiguous, written without the use of jargon, should clearly state the what constitutes a pass and a failure, and should be traceable back to statements in the Hardware Design Specification, Software Design Specification and Functional Design Specification, as applicable, which can be audited (an audit trail).

Test reports shall be produced and approved by Siemens and also the pharmaceutical manufacturer if required under the contract

Siemens as SI routinely prepare all software, hardware and integration test specifications for its clients, and undertakes / records the tests to the approved procedures. The tests being derived from the corresponding design specifications. These test specifications have to be structured such that they are understood for approval by the client . It is not usual for the client to attend / witness all or any of the lower level testing work, but if requested and /or as stipulated in the contract, Siemens will prepare the tests for attendance by the client. Siemens testing of process control systems for GMP applications are conducted in a secure environment with all work on the system and associated documents monitored and recorded; this so as to ensure control of any action that would put the validation status of the system at risk. The above also applies to the Factory Acceptance Test (see 3.5.7) which is normally a contractual milestone to enable the client to witness full system tests at Siemens premises prior to release of the system and associated documentation for delivery to site.

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System (continued):

3.5.7 Factory Acceptance Test Specification

Client acceptance (witness testing) of the system usually takes place in the supplier's works prior to delivery to site and is therefore often called Factory Acceptance Testing (FAT). Factory acceptance testing follows the supplier's own system integration tests, described above, and is conducted against the Functional Design Specification using a Factory Acceptance Test Specification.

The Factory Acceptance Test Specification is a description of those tests to be carried out which ensure that the complete system (hardware and software) operates as indicated in the Functional Design Specification. This specification should define the testing requirements of the complete system over the whole of its operating range including limits, alarms and boundary testing.

Each test should be clear and unambiguous, written without the use of jargon, should clearly state the what constitutes a pass and a failure, and should be traceable back to statements in the Functional Design Specification which can be audited (an audit trail).

All tests must be witnessed and signed off by Siemens as SI and the client (project manager, client group or nominated representative). Siemens must produce test reports which must be approved by the pharmaceutical manufacturer.

The Factory Acceptance Test Specification and Test Report are normally the responsibility of Siemens, and as a contractual documents must be approved both the supplier and the pharmaceutical manufacturer.

At this stage of the Computerized System life-cycle acceptance testing is carried out for a number of similar but separate reasons, namely:

- Factory Acceptance Testing (FAT)
- Site Acceptance Testing (SAT)
- Operational Qualification

With „common„ test criteria it is possible, indeed advisable to institute a single Acceptance Test Specification that will cover test requirements for the integrated computerized system in both its development and operating environments. With any special or differing requirements to be documented and the impact assessed.

The purpose of the Acceptance Test Specification (ATS) is to provide definition for the Factory Acceptance Test, the Site Acceptance Test and as applicable, operational testing as required by Operational Qualification.

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System

3.5.7 Factory Acceptance Test Specification (continued):

The ATS is a document written and carried out by the supplier, and describes all tests to be performed on the process control computer system. It defines:

- The tests to be performed upon the system.
- The data on which the tests will be performed.
- The expected results from the tests.
- The personnel who will carry out and witness the tests.
- The environment and location in which the tests are to take place.
- The equipment on which the tests are to take place.
- The test equipment needed.
- The test documentation required.

The objective of conducting an ATS is to prove to the pharmaceutical manufacturer that the supplied system functions as specified in the agreed Functional Design Specification, and in the case of Performance Qualification encompassing operational needs as specified in the User Requirements Specifications.

The ATS should include tests covering the following:

- All operational functions of the Functional Design Specification.
- All interactions with, monitoring and control of instrumentation interfaced to the computer system.
- All alarm and error reporting functions.
- Data communication protocols and diagnostics within the system and associated database and networks.

The behavior of the system under a wide range of expected and unexpected input.

The ATS should ideally be prepared by a person other than the System Designer, to ensure that the testing is not influenced by knowledge of the system.

The basis and extent of testing to prove adherence to all specified limits must be documented, clearly identifying the reasons for the decisions made, in order to provide reassurance that the supplier has adequately tested the system.

Factory Acceptance Testing is the first stage of system acceptance and will be performed prior to the delivery of the system to the client. This will be performed typically at Siemens facility and will usually require the presence of the client as a witness to the tests. It is the responsibility of the supplier to ensure that the system will pass the pre-defined tests prior to the witnessed testing (see Section 3.5.6, System Integration Test Specification), this is to minimize time taken during reviews and re-tests.

Siemens will retain records to show that such testing has occurred.

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System

3.5.7 Factory Acceptance Test Specification (continued):

It is imperative that the extent of the FAT is maximized, this has the advantage of reducing the risk of problems arising during IQ, OQ and PQ. Problems detected at site are invariably more difficult and time consuming to rectify.

The ATS can contain a large number of tests. It should therefore be structured in a way that will permit easy referencing to the functions specified in the Functional Design Specification and User Requirements Specification as applicable.

A number of general guidelines apply:

- Each function specified in the Functional Design Specification (or URS) should be covered by at least one test in the ATS.
- It is the responsibility of the client in collaboration with the suppliers' project team to determine the extent of these tests.
- Each test action should be defined precisely, the tester should always be clear of the action to take and what constitutes a test pass. Vague statements or criteria should be avoided.
- Each test script should have a unique test reference
- Test scripts should not be duplicated.
- The Test scripts should be logically ordered e.g. in the same order as the functions in the Functional Design Specification (and URS), and this ordering method should be clearly explained.
- Details of the involvement of the pharmaceutical manufacturer in the ATS should be agreed at an early stage and should be included in the document.

A suggested structure for the ATS is as follows:

1. Introduction
2. Scope
3. Test Scripts

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System

3.5.7 Factory Acceptance Test Specification (continued):

4. Test Requirements
   - Test Personnel
   - Reference Documents
   - Test Data
   - Test Equipment

5. FDS/URS Cross References

6. Terminology

Siemens as SI routinely prepares full acceptance testing specifications and test reports for the process control system. Siemens recognizes the close similarity of tests carried out in their own preparatory in-house system integration test (see 3.5.6), the Factory Acceptance Test (see 3.5.7) and the Site Acceptance Test (see 3.6.3). Furthermore, Siemens recognize that the level and type of testing normally employed for the computerized system in the Operational Qualification and Performance Qualification phases have similar requirements, and therefore Siemens is able to provide an Acceptance Test Specification that can be used in full or in part for all these activities, enabling uniform testing, reporting and record of the system.

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System (continued):

3.5.8 Instrumentation Factory Inspection and Calibration Specification

This specification shall define the agreed procedures, test equipment, records and approval requirements for factory inspection and calibration of measurement and control instrumentation.

All calibration test equipment must be traceable back to agreed National Standards.

Calibrated instruments must be provided with a full calibration certificate which details limits of uncertainty and test results.

When agreed in the contract Siemens will provide suitable resource to manage the application engineering, procurement, testing and documenting of the measurement and control instrumentation and any other associated equipment.

3.0 VALIDATION METHODOLOGY

3.5 Construct Computerized System (continued):

3.5.9 Design Review and Report

The overall Design Review at the end of the construction phase is the formal and systematic verification of design activities and is the responsibility of the pharmaceutical manufacturer. It is normally conducted jointly by the pharmaceutical manufacturer and the supplier in order to determine whether the requirements detailed during the definition phase are completely covered by the succeeding system specifications and implementation. It is a technical and quality review of the final process control system design and documentation prior to delivery to, or installation on site (also see APPENDIX NO. 8). A review of the GMP Compliance / Validation Project Risk Analysis should undertaken at this time and included as a section in the design review report.

Considering the activities associated with software design and testing, (and the application engineering and drawings) it is recommended that multiple reviews be conducted throughout the design and construction phases (e.g., at the end of each software life-cycle activity, in preparation for proceeding to the next activity).

Conducting these in-phase design reviews would normally be the responsibility of Siemens, with the level of client involvement to be agreed with the pharmaceutical manufacturer.

Both the pharmaceutical manufacturer and the supplier should have a procedure to enable the design review to be conducted in a consistent and thorough manner. A review should be documented, indicating the actions taken during the review, such as to provide verification through defined procedures and support documentation that the individual elements of the system have been designed and proven so that the integration of the individual parts (including software into the hardware), and all required interfaces (or connected instrumentation) meet the needs of the URS, FDS and Quality Plan.

In order to validate a system it is necessary to know how the system is intended to perform. Sufficient documentation must be developed to confirm how the system is intended to perform. Ideally, the design qualification documentation should be developed concurrent with the system.

Following a successful review meeting, a Design Review report and certificate should be prepared by the pharmaceutical manufacturer and signed by designated members of the validation team. Conditional on satisfactory on-site integration and acceptance testing the Computerized System is available for the Qualification Phases.

An important objective of Design Review is to establish an auditable system of documentation which can be easily maintained throughout the computerized system life-cycle, and ensure approved and controlled transition to the Integrate / Install, and Qualification Phases.

Siemens as SI routinely participates with their clients in the Design Review, and as necessary will provide all relevant design documentation and personnel to enable the clients review. If requested Siemens can assist the client with preparation of the Design Review Report as an added value service.

3.0 VALIDATION METHODOLOGY

3.6 Integrate & Install Computerized System

3.6.1 On-site Installation, Calibration and Commissioning

Proper integration, installation, and commissioning of a Computerized System is essential to the successful qualification of the system. The procedures employed will depend upon many factors, including the type of system and the application. The procedures to be employed in any specific project should be specified in the Validation Project Plan. Written procedures should be established for any and all activities associated with the installation including documentation requirements. Records should be maintained in accordance with well-defined procedures that spell out what activities need to be recorded, requirements for the record retention period, and storage requirements.

Once the process control system has been assembled and fully tested / approved under the Factory Acceptance Test, it is delivered to the client's site where it must be installed and connected to field cabling and instrumentation ready for engineering commissioning.

Commissioning normally includes the following activities:

- Component Unpacking from Shipping Containers
- System Installation and Power-up
- Testing of Environmental Conditions
- Instrumentation Calibration Checks
- Integration of the Process Control Computer with the
- Field instrumentation (Loop Testing)
- Site Acceptance Testing
- Documentation Review
  - As-built Drawings
  - System Manuals
  - Installation Procedures
  - Installation Test Results
- System Operating Manuals
- Operator Training Program Status
- Handover and Acceptance by the Client

Calibration of the instrumentation will be performed over the complete instrument loop. During each instrument and loop calibration, all data must documented on calibration data sheets and submitted to the client for review, approval, and maintenance.

All calibration test equipment must be traceable back to agreed National Standards and documented in the calibration records.

3.0 VALIDATION METHODOLOGY

3.6 Integrate & Install Computerized System

3.6.1 On-site Installation, Calibration and Commissioning (continued):

Once a computer system is received at the client site, Siemens installs and sets up the system to Siemens Installation Standards. As part of Siemens commissioning practice and to help support their regulated clients' validation requirements, Siemens commissions each of its process control systems in accordance with written procedures. If requested by the client, Siemens will provide site calibration of instrumentation related to the process control system as a value-added service. Calibration of each instrument is completed according to agreed calibration procedures. If calibration procedures are not in place and if requested by a client, Siemens may assist the client in providing all procedures required to perform the calibration. All calibration test equipment will be traceable back to agreed National Standards. To compliment site acceptance testing and if required by the client, Siemens can prepare a suitable Installation Verification Report as part of any site installation, calibration and associated documentation supply.

3.0 VALIDATION METHODOLOGY

3.6 Integrate & Install Computerized System (continued):

3.6.2 Site Acceptance Test Specification and Report

Site Acceptance Testing at the clients site is usually required to be conducted on a fully installed computerized system to check that the computer system operates satisfactorily when connected to field instrumentation and cabling. The testing also provides an opportunity to identify and correct any problems due to shipping, utility hook-up and installation / set-up. The SAT is usually conducted prior to or during the validation IQ phase depending on the system complexity and the extent of common activities and documented checks. The degree of SAT required will be determined by the completeness of the FAT and as such is a full or part repeat of the Acceptance Test Specification but with connections to the field devices. The testing will have the same basic format, and specify the same format for recording results, with an agreed level of testing with process equipment (Controlled Function) to include appropriate simulation of process sequence and other operating conditions.

The level of testing at this stage should be such as to demonstrate satisfactory operation of the system functions in conjunction with the dynamics of the process equipment; this will allow Operational Qualification (which is the prime validation task at this stage), to commence with a high level of confidence and at minimum risk to the validation program. This means the SAT normally pre-dates OQ, although it is not unusual for the Pharmaceutical Manufacturer to elect to combine the activities when there is sufficient confidence in the system and process operation.

The SAT should not commence until the client has accepted that the FAT has been conducted satisfactorily. All SAT test results to be analyzed and compared to the FAT results.

Whenever connections to measurement and control instrumentation are utilized in SAT, testing should not proceed until it is ensured that the instruments have been previously inspected and calibrated.

SAT should cover critical routines such as shut down, Critical Process Data manipulation, robustness of Critical I/O, network data checks, system diagnostics and fullest process simulation of automatic sequencing and process alarms as possible.

In some instances Installation and Operational Qualification procedures may be planned to be executed in conjunction with some of the engineering commissioning activities. If this approach is taken, emphasis should be placed on avoiding duplication of efforts. Site acceptance testing / commissioning documentation should be used to compliment the Installation and Operational Qualification documents.

However, a considered approach for qualification of the system is to begin the Installation and Operational Qualification exercises after the site acceptance testing / commissioning has been completed. If the commissioning has been thorough and appropriately documented, then validation should proceed smoothly and where agreed, a number of qualification verifications and tests may reference Siemens commissioning documentation in lieu of duplicating the effort (it is recognized that the definition and contractual standing of SAT can vary, thus the relationship between OQ and SAT herein is intended to present an unambiguous approach in support of the validation program).

3.0 VALIDATION METHODOLOGY

3.6 Integrate & Install Computerized System

3.6.2 Site Acceptance Test Specification and Report (continued):

Important objectives of Site Acceptance Testing are:

1. To support an auditable system of documentation which can be easily maintained throughout the computerized system life-cycle.

1. To establish and record satisfactory engineering commissioning in support of the Design Review and to release the computerized system for Qualification.

Once a computer system is received at the client site, Siemens installs and sets up the system to Siemens Installation Standard. At this time, selected site acceptance tests would be executed and reviewed. This testing to be thoroughly documented and to include the test procedures used, acceptance criteria, data generated, results, individual(s) conducting the test, test date, and all corrective actions for deficiencies that are identified. This testing can be limited based on the degree of disassembly for shipping and re-assembly upon delivery, the complexity of the system, and the cGMP impact of the system.

Siemens as SI documents all site verifications and acceptance tests performed. This documentation provides evidence that the system is installed properly and that the system is operational. This documentation includes, but is not limited to, the following:

- Hardware Installation Verification
- Software Installation Verification
- Point Check Out (Digital Input, Digital Output, Analog Input, Analog Output) Verification
- Network Operational Testing
- Access Security Test
- Alarm Reporting Test
- Report Generation Test
- Control Loops Test
- Loss of Power Simulation
- Activation of Safety Devices
- Computer system diagnostic tests

In addition, Siemens as SI will conduct a review of all system documentation supplied e.g., manuals, procedures, drawings, software programs, component cut-sheets, to ensure that all deliverables required under the contract are available. As required, Siemens can prepare a suitable Site Acceptance Test Report detailing analysis of the acceptance test results. Site Acceptance Testing of the computerized system would normally be a contractual responsibility of Siemens. However, considering the implications of the system integration with the process plant (Controlled Function) not of their supply, the SAT would need to be carried out jointly with the pharmaceutical manufacturer.

On satisfactory completion of the SAT the computerized system will be considered as commissioned. Siemens as SI will prepare a suitable Site Acceptance Test Report in-line with the Acceptance Test Specification (see 3.5.7) and to compliment the Qualification Protocols (see 3.7.4 and APPENDIX NO. 9).

3.0 VALIDATION METHODOLOGY

3.6 Integrate & Install Computerized System

3.6.2 Site Acceptance Test Specification and Report (continued):

Based on satisfactory completion and approval of site acceptance testing, the computerized system (process control system integrated with the field instrumentation and controlled function) can be released for qualification by the pharmaceutical manufacturer.

3.0 VALIDATION METHODOLOGY

3.6 Integrate & Install Computerized System (continued):

3.6.3 Project Validation File

Typically, the following documentation from the Design, Construct, Integrate and Install Phases, complete with all Acceptance documents, should be prepared by Siemens as SI for inclusion in the Project Validation File:

- Supplier Quality Plan, defining the quality issues associated with the provision and control of documentation produced during the development phase of the project.

- Requirement Specification Review Report

User Requirements Specification Revision, consisting of any revisions to the URS following Requirement Specification Review.

- Manufacturing Data Specification Revision, consisting of any revisions to operational data and process parameters (including critical process data) following Requirement Specification Review.
- Schedule of Engineering Drawings, listing all engineering drawings and where they can be located, if not present in the Project Validation File. These to include:
- A complete and accurate Pipe and Instrumentation Diagrams (P&IDs) which indicate all system components, along with component tag names. (The P&IDs provided by the pharmaceutical manufacturer should include a cover sheet which indicates all symbols used to represent components and connections. However, for most secondary process equipment and packaging systems P&IDs may not be available. In this case I/O listing and functional description are expected.)
    - Cabling and wiring diagrams
    - Loop Hook-ups, including electro-pneumatic conversion detail.

- Schedule of Materials and Equipment, describing all materials and equipment to be provided as part of the process control system.

- Schedule of Engineering Specifications and Standards, listing all the requirements for the manufacture / fabrication / supply of equipment and where they can be located, if not present in the Project Validation File.

- Schedule of measurement and control Instrumentation data sheets and where they can be located, if not present in the Project Validation File.

3.0 VALIDATION METHODOLOGY

3.6 Integrate & Install Computerized System

3.6.3 Project Validation File (continued):

- Schedule of Supplier Documentation, listing all supplier documentation and where it can be located, if not present in the Project Validation File. This to include:
  - System design and test specifications, test results and reports.
  - A complete annotated input/output (I/O) listing (analog and digital), along with an application source code cross-reference indicating all process control system registers, timers, counters, etc.
  - A complete and fully commented copy of the application source code in hard copy form (electronic copies of the source code may also be required).
  - A system architecture diagram, along with a listing of all measurement and control instrumentation, plus any components supplied by others as part of the computerized system and not identified on the architecture diagrams.
  - A description of operations which describes all modes of operation (e.g., start-up, shutdown, manual/automatic), indicating all alarms with limits, actions, and responses.
  - A complete and accurate listing of each process graphics screen for each workstation which includes all I/O points being displayed.
  - Any specific requirements for the system which have been defined by the client.
  - Hardware and Software Manuals, to include but not be limited to system I/O modules, CPU, programming, database, security, setup and configuration.
  - Network adapters.
  - Backup software, to include but not be limited to current operating system, system programs/files, network interface software.
  - Comments and symbols for application files

- Schedule (showing status) of SOPs for Operation, Security, Backup, Data Archiving

- Spare parts listing for hardware components

- Schedule of Exclusions / Changes / Concessions, listing all exclusions, changes and concessions and where they can be located, if not present in the Project Validation File.

- Schedule of Validation Communications, listing all communication documents relating to validation issues and where they can be located, if not present in the Project Validation File.

- Schedule of Fabrication, Inspection and Calibration certificates / drawings, listing each certificate / drawing and where they can be located, if not present in the Project Validation File.

- Schedule of Factory Acceptance Tests, listing each test specification / result and where it can be located, if not present in the Project Validation File.

- Schedule of Site Acceptance Tests, including installation verification reports, listing each test specification / result and where it can be located, if not present in the Project Validation File.

3.0 VALIDATION METHODOLOGY

3.6 Integrate & Install Computerized System

3.6.3 Project Validation File (continued):

Schedule of system utilities inspection and testing, e.g. electrical power supply and distribution installation and testing in accordance with all local and national codes, and where it can be located, if not present in the Project Validation File.

- The Design Review Report (with all associated DQ review meeting minutes, including review of the GMP Compliance / Validation Project Risk Analysis).

- The Release for Qualification certificate (with any associated reservations).

Information which cannot easily fit into the Project Validation file (e.g. standard system manuals etc.) may be filed elsewhere and a reference sheet provided in the appropriate section of the Project Validation File identifying the information and stating where it can be found.

All documentation provided by the supplier must be clearly marked so as to be easily cross-referenced its location in the Project Validation file with the pharmaceutical manufacturer's Inquiry package and document requirement matrix. It is considered acceptable practice to have documented record of test strategy, plans and results archived by the supplier. There is no stipulated retention period, but this should be agreed with the pharmaceutical manufacturer.

Siemens as SI is responsible for maintaining the up-to-date-status of the Project Validation File, and the provision of their own design specification, testing and installation drawings and documentation. Under the contract Siemens may also have to control project validation documents related to the computerized system that are to be prepared by the client and others. Siemens in conjunction with the client prepare a validation document matrix to identify all levels of validation documentation to be held in the Project Validation File (or by Siemens) and those responsible for preparing, approving, maintaining and implementing the documents. To control this activity Siemens in conjunction with the client will agree a Document Control system, which Siemens will institute and manage, handing over to the client on contract completion. Siemens acknowledges that this is a vital area for securing validation documentation and as such recognize that it will be subject to internal audit throughout the project by both the client and Siemens themselves.

3.0 VALIDATION METHODOLOGY

3.7 Qualify Computerized System (continued)

3.6.4 Qualification of Systems

Qualification is the procedure of collecting appropriate data that, when documented properly, provides a high level of assurance that a Computerized System will operate in accordance with the system specification. The specific approach to be used in the qualification of a Computerized System should be described in the Validation Project Plan and the applicable validation SOPs. While there are no absolute lines to be drawn between the different types of testing typically performed in the qualification of a Computerized System, it is convenient to identify two types of qualification testing that assure that the system is installed properly and that it operates properly: Installation Qualification and Operational Qualification. Documented procedures for preparation of qualification protocols and implementation of qualification protocols are necessary.

The specific approach to be used in the qualification of a Computerized System should be described in the Validation Project Plan and the applicable Validation SOPs. Depending on the application Qualification of complex Computerized Systems may require the division of the computerized system into sub-systems, each of which can then be qualified separately. Once the sub-systems of a complex Computerized System have been qualified, the qualification of the integrated system will be a more reasonable task. It may also be desirable to qualify the system and the process as separate protocols or as one, integrated Qualification Protocol.

An important objective of Qualification review and reporting is to establish an auditable system of documentation which can be easily maintained throughout the computerized system life-cycle, and ensure an approved and controlled, fully documented transition to subsequent validation phases.

The computerized system Functional Design Specification, including subsequent lower level design specifications (i.e. hardware and software specifications) is the primary reference for Qualification Protocol development. Clear system specification will yield detailed acceptance criteria for specific functional testing. The functional testing implemented during system integration and acceptance testing should also be utilized to support the qualification effort and to optimize the resource required to achieve validation. By working closely with the client, this will minimize repetitive or unfocused functional testing.

While there are no absolute lines to be drawn between the different types of testing typically performed in the qualification of a Computerized System, it is recognized that three (3) types of qualification testing will best assure that the system is installed properly, that it operates properly, and that it performs as specified in its operating environment (see 3.7.2, 3.7.3 and 3.8.1).

3.0 VALIDATION METHODOLOGY

3.7 Qualify Computerized System (continued)

3.6.5 Installation Qualification (IQ)

Installation Qualification of a Computerized System is documented verification that system design and configuration are as intended, .that instrumentation has adequate accuracy, precision and range for intended use, that services (such as electrical power) are of adequate quality / reliability, and that there are appropriate system manuals, as-built drawings, instrument calibration reports, and SOPs on the operation of the system.

An IQ protocol which describes how the hardware and software (and control and measurement instrumentation) is to be installed and qualified, is required.

In practice, for computer hardware, peripheral equipment (e.g. printers) and instrumentation the Installation Qualification (IQ) is to ensure that all equipment is installed and calibrated as required, and that sufficient documentary evidence exists to demonstrate and maintain this.

IQ of software includes verifying that the proper version of the program has been installed properly and that appropriate backup copies exist, and that all required software is installed. In practice for software the Installation Qualification (IQ) is to ensure that the software is installed according to suppliers recommendations, and that sufficient documentary evidence exists to demonstrate this. The software IQ should cover system software (operating systems, communications software etc) and application software (including interfaces). Evidence that installation of the application software has been successful is provided by retention of all installation documentation, installation instructions and shipment memorandum as appropriate. Additional evidence can be provided by the retention of job logs created at the time of loading the software.

Examples of documents / data generated for the IQ:

- Installation Qualification Protocol
- Installation Qualification Results
- Installation Qualification Report

3.0 VALIDATION METHODOLOGY

3.7 Qualify Computerized System (continued)

3.6.6 Operational Qualification (OQ)

Operational Qualification (OQ) is the name given to the technical and quality review and testing of the commissioned computerized system connected to, and operating process / product manufacturing equipment. The system includes the process control system, control and measurement instrumentation, and all associated interfaces including those to higher level systems.

An Operational Qualification Protocol which describes the qualification requirements i.e. full operational testing and support documentation is required.

The purpose of the review is to verify through defined procedures and support documentation that the computerized system meets the operational and functional requirements defined in the Functional Design Specification. Here, verification should be considered as including full re-testing of the system, unless previously conducted acceptance tests, e.g. SAT, are accepted and approved for inclusion as an integral part of OQ.

The OQ would not normally commence until the client has accepted that the SAT and IQ has been conducted satisfactorily. The specification for OQ should ensure full testing of the measurement and control instrumentation.

Conditions which are to be satisfied prior to start of OQ should be stated in the test plan. It is suggested that such details should include assurance that all system hardware, software, and networks / interfaces (and measurement and control instrumentation) are available and have been satisfactorily acceptance tested, and that all post-installation documentation is available.

OQ includes the identification of all critical operating parameters, their anticipated ranges, appropriate acceptance criteria. This is comprehensive testing during the OQ phase to ensure that the computer system, connected to the manufacturing process via field devices, functions correctly to enable plant operation. Demonstration of secure data acquisition and control of „raw process data„ is particularly important for this level of qualification.

It is important that all test equipment or test software required are explicitly stated / recorded in the relevant Acceptance Test Specification.

There may be one or more Operational Qualifications for a given validation depending on the scope of the system. For computerized automation systems, the OQ is usually conducted with a „dry run„ and / or a „wet run„ the latter using some representative media.

Examples of documents / data generated for the OQ Phase are as follows:

Operational Qualification Protocol (including test procedures and expected results)
Operational Qualification Results
Operational Qualification Report

3.0 VALIDATION METHODOLOGY

3.7 Qualify Computerized System (continued)

3.6.7 Qualification Protocols

Qualification Protocols are written and approved documents that are prepared in advance of testing and describe the objectives of the test and the pre-approved test methods and acceptance criteria to be followed. Qualification Protocols specify who is responsible for conducting the tests, what specific method is to be used for each test, how data are to be collected and reported, and what review and evaluation procedures will be used to determine if the acceptance criteria are met (see APPENDIX NO. 9).

Acceptance criteria will be based on the respective level of computerized system specification (see Qualification „V„ Plan in Figure 3).

The pharmaceutical manufacturer is responsible for Qualification Protocol preparation and implementation.

If requested by a client, Siemens as SI will provide assistance with qualification protocols and qualification activities as a value-added service. This assistance may be in the form of assistance with the qualification protocol preparation, implementation, review and support documentation. In particular cases, Installation Verification and Site Acceptance Testing documentation may be utilized or referenced in lieu of qualification testing provided the documentation is accurate and complete. This cost and time effective assistance may prevent duplication of efforts.

3.0 VALIDATION METHODOLOGY

3.7 Qualify Computerized System (continued)

3.6.8 Qualification Summary Reports

Summary Qualification Reports are written and approved documents that are normally prepared by the pharmaceutical manufacturer and present an analysis of the results of the tests that were conducted in accordance with Qualification Protocols. Qualification Reports compare test data against acceptance criteria and state clearly the basis for concluding that system performance is found acceptable. The reports include summary data displayed in a format that allows findings to be clear. Use of tables, graphs, and charts is customary, and the results presented in such summary form should be checked for accuracy and completeness.

The report reviews the results, draws conclusions and makes recommendations for future actions (as necessary). These may take the form of corrective actions in the event of a test failure, or additional procedures if use of this part of the system is conditional. The qualification report and conclusions should be approved by the same signatories that approved the protocol.

The client's Validation SOPs and a Validation Project Plan specify whether separate or integrated Qualification Protocols and summary Qualification Reports are to be prepared for IQ, OQ (and PQ). They also specify the personnel responsible for reviewing and approving Qualification Protocols, test data, and summary Qualification Reports. The significance of each approval signature in reflecting the nature and extent of reviews and evaluations will be defined in writing.

During qualification testing it is typical to encounter instances where the acceptance criteria for a particular qualification verification or test is not met. This is referred to as a deviation. The degree and quantity of deviations is directly proportional to the quality of the vendor's design, development, system build, integration, and testing practices and procedures. Since qualification testing takes a somewhat different approach to commissioning, it is required that deviations are identified and documented.

A suggested structure for a qualification report is as follows:

- Cover page (including company identification and unique report number and references).
- Signatories (Identification and Authority of author and approvers)
- Introduction (objectives and methodology)
- Results Review (test status)
- Discrepancies (resolved, outstanding, resulting actions)
- Conclusions and Recommendations

Test results must be clearly categorized as CONDITIONAL PASS, PASS or FAIL.

3.0 VALIDATION METHODOLOGY

3.7 Qualify Computerized System

3.7.5 Qualification Summary Reports (continued)

Report conclusions for the execution of a qualification protocol for a computerized system should be clearly stated as UNCONDITIONALLY APPROVED, CONDITIONALLY APPROVED or NOT APPROVED, with appropriate reference to any conditions.

At this time a review of the GMP Compliance / Validation Project Risk Analysis should be undertaken and included as a section in each Qualification Summary Report.

Siemens as SI can perform a value-added role in addressing deviations. Working with the client as part of the Validation Team, Siemens can assist in analyzing deviations and identifying / recommending / conducting approved corrective actions. Resolutions may be in the form of reprogramming, debugging, and documentation support.

3.0 VALIDATION METHODOLOGY (continued):

3.7 Evaluate in Operating Environment

3.7.1 Performance Qualification (PQ)

Performance Qualification of a Computerized System is the third type of qualification as provides documented verification that the total integrated Computerized System in its Operating Environment performs in accordance with the User Requirements Specification throughout the intended operating ranges. The total system includes all hardware and software components, associated process equipment, control and measurement instrumentation, operating personnel, and procedures that make up the system (also see APPENDIX NO. 9).

A Performance Qualification Protocol must be produced and conducted by the pharmaceutical manufacturer. Procedures governing the use of the system must be written prior to execution of the protocol. The protocol should then be executed, the results recorded and a summary report should then be written (see 3.7.5).

PQ is normally conducted in conjunction with actual product / data, and it is common practice for the pharmaceutical manufacturer to undertake a minimum of three (3) satisfactory „validation runs„ to achieve PQ. When a product is being produced, PQ includes verification that the Computerized System consistently produces a product meeting its pre-determined specifications and quality attributes.

Examples of documents / data generated during the PQ Phase include:

- Performance Qualification Protocol (including test procedures, data and expected results)
- Performance Qualification Results
- Performance Qualification Report
- Operating Procedures

Siemens clients are responsible for Qualification Protocol preparation and implementation (also see 3.7.4).

If requested by a client, Siemens as SI will provide qualification assistance as a value-added service. This assistance may be in the form of assistance with the qualification protocol preparation, implementation, review and support documentation.

3.0 VALIDATION METHODOLOGY

3.7 Evaluate in Operating Environment (continued)

3.7.2 Final Report

On completion of all of the Qualification Protocols and Summary Reports associated with the Validation Project Plan a final report must be prepared by the pharmaceutical manufacturer's Validation Team; this is sometimes referred to as the Validation Summary Report. The objective of the report is to give an overview of the results of the execution and draw a conclusion as to the suitability of the computerized system for use. This may be unconditional use or there may be restrictions associated with the systems use. In the latter case the proposed remedial action must be referenced, and when this includes changes to the system there must be a proposed schedule.

The report usually addresses the issues identified by the Validation Project Plan, to provide easy cross reference for compliance. The report should review the key documentation associated with the various steps of the validation project and preview the on-going support activities required to maintain validation.

At this time a review of the GMP Compliance / Validation Project Risk Analysis should be undertaken and included as a section in the Final Report.

A suggested structure for a Final Report is as follows:

- Cover page (including company identification and unique report number and references).
- Signatories (Identification and Authority of author and approvers)
- Introduction (objectives and methodology)
- Results Overview (Test type status)
- Deviations / Discrepancies (resolved, outstanding, resulting actions)
- Conclusions and Recommendations

Test results must be clearly categorized as CONDITIONAL PASS, PASS or FAIL.

Report conclusions of the execution of the Validation Plan and for the satisfactory operation of the Computerized System in its operating environment should be clearly stated as UNCONDITIONALLY APPROVED, CONDITIONALLY APPROVED or NOT APPROVED, with appropriate reference to any conditions.

The Final Report, authorizing use of the computerized system should not be issued until all support requirements have been put in place. It is vital that the validation status of the system is not compromised.

The pharmaceutical manufacturer must also set a regular review (e.g. annual) based on the Phase / Periodic Review procedure.

3.0 VALIDATION METHODOLOGY

3.7 Evaluate in Operating Environment (continued)

3.7.3 On-going Evaluation

The purpose of On-going evaluation (sometimes called Maintenance Qualification or General Qualification) is to ensure that the system maintains its validated status by developing procedures governing the use of the system.

Written procedures shall define how systems will be evaluated on an on-going basis over the life cycle of the system. The procedures should define responsibilities for review and should follow pre-determined criteria. When reviews detect conditions or practices that deviate from pre-determined criteria, then investigations and corrective actions should be undertaken. Periodic evaluations should take into account all relevant sources of information and data that demonstrate the suitability of system performance including, but not necessarily limited to:

- Trend analysis
- Errors
- Deviations/Discrepancies/Failures (Investigations)
- Reworks-Reprocessing
- Product failures
- Analytical testing failures
- Software/Hardware changes
- Process failures
- Client complaints
- Any other condition influencing the validated state

An important objective of On-going Evaluation is to maintain an auditable system of documentation throughout the computerized system life-cycle, and ensure an approved and controlled, fully documented record of any activity that will affect the validation status of the Computerized System and the Process it is integrated with.

On-going Evaluation can be considered under the following headings:

- Procedures
- Training
- Maintenance Plan
- Evaluation Summary Report

It should be noted that a number of validation procedures apply to activities performed throughout the validation program. Siemens may be involved with a number of the activities governed by these SOPs.

3.0 VALIDATION METHODOLOGY

3.7 Evaluate in Operating Environment

3.7.3 On-going Evaluation (continued)

3.7.3.1 Procedures

SOPs provide detailed instructions for executing specific tasks or assignments, and establish clearly which operations need to be documented, what information the documents should contain, how critical information should be verified, who is responsible for generating the documentation, and what approvals are required for each document. This in accordance with the pharmaceutical manufacturer's procedure for writing and approving SOPs.

FDA requires pharmaceutical manufactures to maintain SOPs for all actions or activities that could impact on the quality, safety, identity, or purity of a pharmaceutical product. Each SOP must give specific instruction on how to perform certain actions. There must be SOPs for all of the actions necessary to satisfy the requirements of the applicable policies and to ensure that the activities are carried out in a uniform and reproducible manner.

Each of the following procedures is applicable to the computerized system and must be documented. The procedures must be approved by quality control and the department in which they are used, and all operatives must be trained in their use.

Procedures required for Computerized System On-going Evaluation include the following:

Validation Procedures:

- Periodic Review
- GMP Compliance and Risk Assessment
  - Document Management
    Production
    Review / Approval
    Issue / Withdrawal
    Changes
    Master Document File
  - Deviation Analysis / Corrective Action
  - Change Control Procedures
    Software
    Hardware Upgrade / Replacement
    Configuration
    Data
    Documentation

3.0 VALIDATION METHODOLOGY

3.7 Evaluate in Operating Environment

3.7.3 On-going Evaluation

3.7.3.1 Procedures (continued)

- Configuration Management
- Hardware / Software Inventory Review
- Internal Audit
- Training

- Role and Responsibility of Quality Control
- Validation Process Modification
- Contractor Control
  - Business Continuity Planning
    Contingency Plans
    Disaster Recovery Procedure
  - Maintenance
    Maintenance Programs / Schedules
    Calibration
  - Decommissioning Procedures

Computerized System Operating Procedures:

- System Management Procedures
  - Daily Operations
  - Back-up
  - Restore
  - Purge
  - Storage / Archive / Retrieval
  - Job Scheduling
  - Log Review
- System Operating Procedures / Manual
  - Start-up and Shut-down
  - Application procedures
  - Data Entry and Verification
  - Peripherals
- System Security Procedures
  - Operating System Security
  - Physical Security
  - Application Security

3.0 VALIDATION METHODOLOGY

3.7 Evaluate in Operating Environment

3.7.3 On-going Evaluation

3.7.3.1 Procedures (continued)

A number of these procedures are also necessary in the earlier phases of the validation program, e.g., Deviation and Corrective Action, Review and Approval, Change Control, Document Management, GMP Compliance and Risk Analysis.

Siemens as SI would normally be contracted to supply (or assist in developing) the system operating procedures. As a value-added service, Siemens may be requested to assist clients in developing selected * Validation SOPs required to support the on-going evaluation of computerized systems. In addition, through various client-specific Technical Support Agreements, Siemens may assist clients with maintenance support, calibration support, and troubleshooting services.

3.0 VALIDATION METHODOLOGY

3.7 Evaluate in Operating Environment

3.7.3 On-going Evaluation (continued)

3.7.3.2 Training

For each procedure identified as required for the system under consideration there should be documented evidence that the persons affected by the procedure have been trained in its use.

Training is also necessary on the validation methodology being used and on GMP requirements as relevant.

It should also be noted that all persons (including the supplier, contractors, consultants) involved in the validation program itself must be trained to a suitable level. The supplier should ensure that suitably trained personnel are used on pharmaceutical projects. Project personnel should be qualified on the basis of appropriate education, training and / or experience in the type of computerized system to be used and in recognized software and hardware development methods. Key members of the supplier's project team should be knowledgeable in those levels of regulatory requirements that affect a computerized system.

As required Siemens can identify training needs for pharmaceutical applications, and provide appropriate training to enable the client and Siemens project personnel to be suitably qualified for the application and its operation. Siemens if requested can also assist in developing and implementing training programs for the pharmaceutical manufacturer.

Maintenance Plan

The Maintenance Plan is intended to replace the project level quality plan in support of the On-going Evaluation and recognizes that support issues are different to development issues.

This procedure normally applies to those systems (or parts of systems). that are to be supported by the supplier, but can include activities to be undertaken by the pharmaceutical manufacturer. The Maintenance Plan is therefore normally written by the supplier and can form the basis of a formal support contract. The plan needs to define the scope of maintenance, i.e. items to be maintained, the type of activities, the period of the contract, access requirements, procedures to be followed in conducting / recording / reporting maintenance, and the resource / response times.

Siemens as SI will identify computerized system maintenance needs for pharmaceutical applications, and can provide appropriate maintenance programs to ensure the computerized system is maintained satisfactorily. Siemens if requested can assist in developing and conducting maintenance on both the computer system and the measurement and control instrumentation.

3.0 VALIDATION METHODOLOGY

3.7 Evaluate in Operating Environment

3.7.3 On-going Evaluation (continued)

3.7.3.3 Evaluation Review and Summary Report

After a defined period of operation, an Evaluation review will be carried out on the manufacturing process, including the computerized system and its associated control and measurement instrumentation. This review will be prompted by the validation status review program for the process located in the site validation master plan.

The purpose of the review, with regard to the computerized system and associated measurement and control instrumentation, is to verify that it has been maintained in a validated condition since either the last review or since PQ, whichever is the most recent. This is achieved by examining the documentary evidence available.

The documentation gathered for the review should include evidence (signatures, etc.) to ensure that as a minimum the following are conducted and documented:

Supporting documentation should cover activities which either directly or indirectly affect the operation of the system. Particular attention should be given to the control of changes and test records.

- Review of the actions identified during the last validation or qualification review meeting and their current status.

- Review of all applicable change notices since the last review to ensure the site change control procedure and quality system have been properly implemented. This should include an audit of all affected documentation, their revision and approval and all subsequent actions (i.e. details of the actual change itself).

- Review of any major modifications and associated re-validation activities necessary to bring the system back to its PQ status. This should include a review of all change notes raised, an audit of all affected documentation, their revision and approval, and all subsequent actions (i.e. details of the actual change itself).

- Review of the operator and maintenance log books to ascertain any recurring problems, either with the system or the process, in order to decide on the action to be taken.

- Review of the calibration data for all measurement and control instrumentation, and any applicable parts of the operational control system, to ensure site calibration procedures have been followed. The review should include an agreement on the frequency of calibration necessary for these items.

- Review of any training received by operations and maintenance personnel during the period and identification of training needs for the next period.

3.0 VALIDATION METHODOLOGY

3.7 Evaluate in Operating Environment

3.7.3 On-going Evaluation

3.7.3.3 Evaluation Review and Summary Report (continued)

- Review of any new operational SOPs generated since the last review and/or any changes to existing operational SOPs found necessary through use.

- Review of Data which demonstrates that the operating environment for the system is within the manufacturers' limits.

- Review of the GMP Compliance / Validation Project Risk Analysis

- Review of all other procedures, actions and records identified in 3.8.3.1 above.

An Evaluation review meeting summary report should include the review process, documents reviewed, comments from attendees and the collectively agreed course of action.

The Evaluation review meeting report should also include a schedule itemizing any documentation which requires updating and those responsible for completing this work. The progress of updates should be monitored through the documentation management system against agreed completion dates.

Following a successful review meeting, an Evaluation review certificate should be prepared by the system owner and signed by designated members of the validation team.

The validation status review program for the system in the Validation Master Plan should be updated with the date for the next review meeting.

The Evaluation review certificate and review report should be retained in the validation file for the computerized system.

3.0 VALIDATION METHODOLOGY

3.7 Evaluate in Operating Environment (continued)

3.7.4 Validation File

Together with the Project Validation File, the key validation documentation from the Planning, Definition, Supplier Selection, Qualification and Evaluate steps (see APPENDIX NO. 2) can be filed under document control and make-up a Computerized System Validation File (or Manual). This master file, supplemented by on-going evaluation documents would enable effective control and efficient access at all times. This being particularly useful during inspections by regulatory authorities.

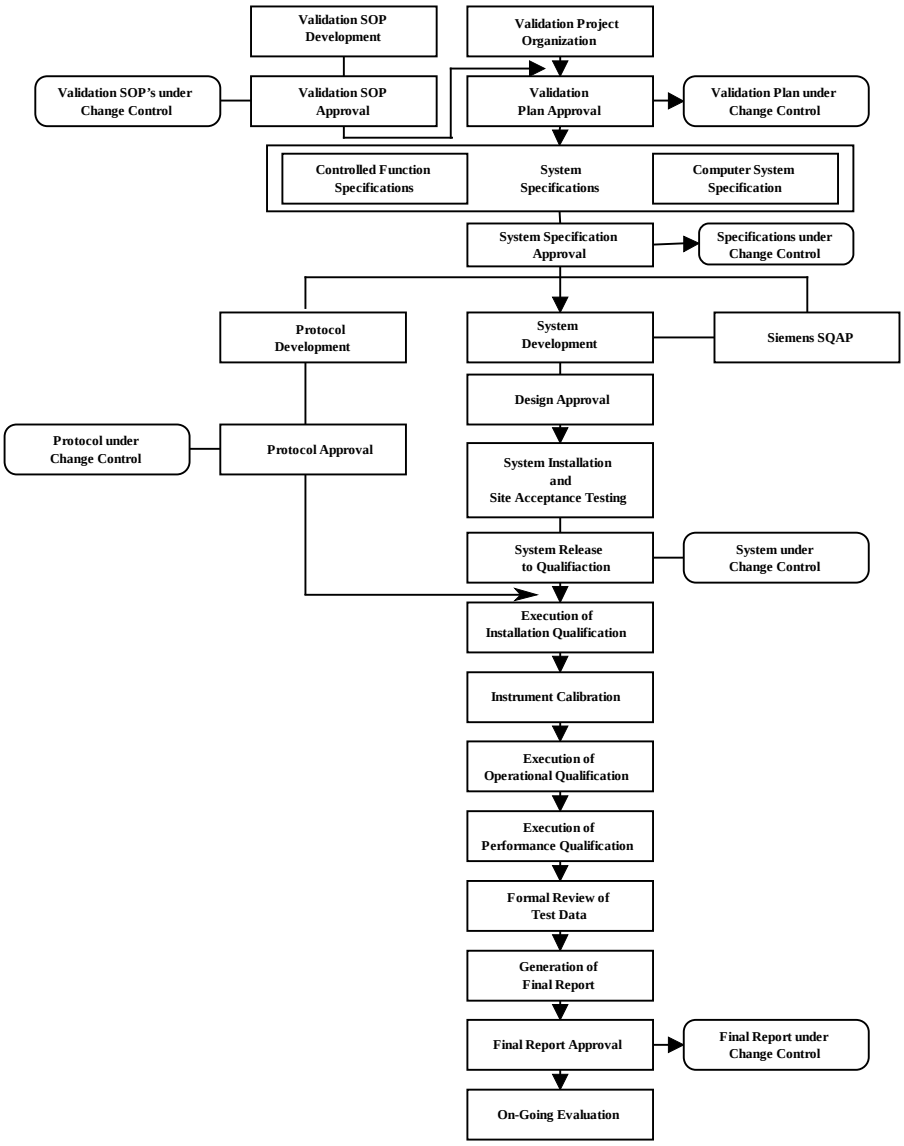
Consideration should be given to structuring the Computerized System Validation File so as to reflect the validation life-cycle, for example:

- Introduction [Site, Plant, Process(es), Product(s)]
- Planning [Validation Policies, Plans and SOPs]
- Definition [System and Manufacturing Requirements / Data]
- Select [Supplier audit and selection]
- Design [System Specifications and SOPs]
- Construction [Development and Testing]
- Integrate and Install [including Acceptance Testing]
- Qualification [IQ, OQ, PQ]
- On-going Evaluation [Reports]
- SOPs [Operations, System, Support Procedures]
- Appendices [Quality System, Working Methodologies, Risk Analysis]

4.0 VALIDATION MILESTONES

Throughout a computerized system validation project Validation Milestones will be encountered. In most cases these milestones involve the approval of key documentation with respect to the validation effort. All instructional, event and record documentation are to be processed under document control and held in the appropriate validation file. These Validation Milestones are represented in Figure 6 (also see 1.3.5) .

Figure 6. Validation Milestones



4.0 VALIDATION MILESTONES (continued):

4.1 Validation Project Organization

The first important milestone for the validation effort is the selection of Validation Team members. A Validation Team should consist of representatives from a variety of disciplines including Validation, Quality Assurance, Engineering/Technical Services, Manufacturing, Regulatory, Information Technology (and on contract award at the project level, the supplier of the Computerized System). The initial tasks the Validation Team need to conduct include project definition and GMP Compliance / Validation Project Risk assessment. On completion and approval of the initial analysis, the Computerized System can be entered on to the Computerized System Inventory as part of the Validation Master Plan, and development of the Validation Project and Quality Plans, and Validation SOPs can commence.

4.2 Validation SOP Approval

The second important milestone for the validation effort is the generation and approval of the Validation SOPs to be utilized on the project. These SOPs include appropriate procedures for change, review and report for all approved documents. The quality control unit of the client will generate and clearly establish the responsibilities for actions relating to these documents. (Computerized System operating procedures will normally be generated in parallel with system design, development and testing for assessment as part of OQ, and in readiness for use under PQ).

4.3 Validation Project Plan Approval

The third important milestone for the validation effort is the generation and approval of the Validation Project Plan. Following approval of the Validation Project Plan, any revisions will be assessed and if appropriate, authorized under the change control SOP.

4.4 Computerized System Specifications Approval

The forth important milestone is the approval of the computerized system specifications which form the cornerstone of the validation effort. These specification documents are based on the reviewed User Requirements Specification (including manufacturing data and test criteria verification), and embrace all system design and test specifications, and pre-qualification acceptance testing. Any revisions to these documents to be evaluated and formally approved by the appropriate personnel under the change control procedure.

4.0 VALIDATION MILESTONES (continued):

4.5 Design Review Approval

The fifth important milestone is the approval and release of the fully tested computer system for installation and integration with its Operating Environment. The Design Review examines all activities, deviations, revisions, support documentation and acceptance testing during the Design and Construct Phases. Establishing satisfactory completion of those phases, recording any conditional and remaining work, including Site Acceptance Testing, to be completed.

4.6 Qualification Protocol Approval

The sixth milestone is the approval of the Qualification Protocols, developed for the process control system and also, as required, for the controlled function. All deviations to be recorded and revisions evaluated and formally approved by the appropriate personnel under the change control procedure.

4.7 System Release to Qualification

Once a Computerized System has successfully completed the SAT it can be released for qualification under the process validation program and the integrated Computerized System is placed under the pharmaceutical manufacturers change control procedures. System changes will be evaluated with respect to their impact on the system specification, and any revision to the software after release must be approved by the appropriate personnel. All documentation of the software will be modified to reflect any changes according to a written procedure.

4.8 Qualifications (IQ, OQ, PQ)

All testing will follow procedures outlined in the approved Qualification Protocols. Any deficiencies found during testing will be recorded and formally reviewed, and an evaluation for appropriate action made. Change control must be utilized if revisions are to be made to approved test procedures.

4.0 VALIDATION MILESTONES (continued):

4.9 Final Report Approval

4.9 Final Report Approval

Once the IQ, OQ and PQ test data are reviewed and their accuracy verified, a Validation Report will be prepared that will summarize the results of the qualifications and present conclusions and recommendations. If a Computerized System is determined as performing satisfactorily in its operating environment, validation will be confirmed and the Computerized System is available for operation / production. Subject to any major changes the Computerized System is now monitored under an on-going evaluation process to ensure its validation status is maintained.

5.0 REFERENCES

5.1 **ISO 9000-3**, *Quality Management and Quality Assurance Standards - Part 3: Guidelines for the Application of ISO 9001 to the Development, Supply, and Maintenance of Software*, International Organization for Standards, CH-1211 Geneva 20, Switzerland, 1991.

5.2 **TickIT Guide**, *A Guide to Software Quality Management System Construction and Certification using ISO 9001, Issue 3,October, 1995.*

5.3 **FDA**, *Guideline on the General Principles of Process Validation*, 1987, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Rockville, MD.

5.4 **FDA**, 21 Code of Federal Regulations, Part 820, *Good Manufacturing Practices for Medical Devices*, as of April 1, 1995.

5.5 **FDA**, 21 Code of Federal Regulations, Parts 210-211, *Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs, as of April 1*, 1995.

5.6 **PDA**, Journal of Pharmaceutical Science and Technology, Technical Report No. 18, *Validation of Computer-related Systems*, Volume 49, Number S1, January/February 1995.

5.7 **Tetzlaff**, Ronald F., *GMP Documentation Requirements for Automated Systems*, Proceedings of the International Congress on Advanced Technologies for Manufacturing of Aseptic and Terminally Sterilized Pharmaceuticals and Biopharmaceuticals, Parenteral Drug Association, Basel, Switzerland, February 1992.

5.8 **GAMP,** *Supplier Guide for the Validation of Automated Systems in Pharmaceutical Manufacture, Version 2.0*, by the Good Automated Manufacturing Practice (GAMP) Forum, May 1996.

6.0 APPENDICES

APPENDICES

APPENDIX NO. 1A VALIDATION MASTER PLAN STRUCTURE

The Validation Master Plan should be reviewed on a regular basis (e.g., annually) and should cover the sections indicated , with a structure that will facilitate updates:

Introduction and Scope
- Document source and signature authority
- Relationship to Company Policy for Validation
- Overview of planning levels within Company
- Plan review schedule

Organizational Structure
- Ownership, Technical Support and Quality Management

Applicable Areas
- Description of Facility, Products
- Area(s) to be addressed
- Critical Process Parameters / Raw Data

Outline of Validation Tools and Controls
- GMP Compliance and Risk Assessment
- Quality Management
- Validation Project Plans
- Standard Operating Procedures
- Prospective Validation
- Retrospective Validation
- Re-qualification
- On-Going Evaluation
- Equipment / System Inventory
- Document Management
- Configuration Management
- Deviation Reporting
- Change Management

Areas or System Lists
- Area list and / or inventory of systems or projects
- Current status
- GMP relevance
- Critical Process Parameters / Raw Data
- Existence of Validation Project Plan(s)

Training Plans

Validation Plan Timeline

References
- Plan review / update procedure
- Validation Process Modification
- Definition of Terms / Abbreviations

APPENDIX NO. 1B VALIDATION PROJECT PLAN STRUCTURE

As the Validation Project Plan will probably be revised during the project it should be structured in such a way that it can easily be updated. The plan should cover the sections indicated, and can be structured as follows:

Introduction
- Document source and signature authority
- Relationship to Validation Master Plan
- Validation scope and objectives
- Plan review schedule

Roles and Responsibilities
- Quality Management
- Production
- Engineering
- IT
- Supplier(s)
- Validation Team

Application
- Application overview
- GMP requirements
- System description

Validation Strategy
- Validation methodology
- Life-cycle model
- Process Validation
- Critical Data Identification
- Acceptance Criteria (incl. appendix)
- Computerized System Specification
- Qualification / Review Approval
- On-Going Evaluation
- Validation Documentation Responsibility Matrix (incl. appendix)
- SOP listing (incl. appendix)

Key Validation SOPs and Support Programs
- Document Control
- SOP Preparation Procedure
- Review and Approval Procedure
- GMP Compliance and Risk Analysis
- Computerized System Inventory Review
- Project and Quality Plan
- Software Quality Assurance Plan
- Supplier Evaluation
- Deviation Analysis / Corrective Action
- Configuration Control

- Change Control
- System Access Security
- Contingency Plan and Disaster Recovery
- Maintenance Plan
- Performance Monitoring
- Contractor Control
- Internal Audits
- Engineering Standards
- Hazard and Operability Study

Training schedule (incl. appendix)

Validation Program
- Validation Milestones
- Resource Estimate

References
- Plan review / update procedure
- Definition of Terms / Abbreviations
- Other relevant documentation

Appendices
- Validation document / responsibility matrix
- SOP List
- Acceptance Criteria
- Training Schedule

APPENDIX NO. 2 VALIDATION DOCUMENTATION RESPONSIBILITY MATRIX

Number	Step	Key Documentation	Responsibility				
			Prepare	**Review**	**Approve**	**Maintain**	**Implement**
1	Plan	Validation Policy	***C***	***C***	***C***	***C***	***N/A***
		Validation Master Plan	***C***	***C***	***C***	***C***	***C***
		Computerized System Inventory	***C***	***C***	***C***	***C***	***C***
		Validation SOPs	***C***	***C[1]***	***C***	***C***	***C***
		Validation Project Plan	***C[1]***	***C[1]***	***C***	***C***	***C***
		Project and Quality Plan	***C***	***C***	***C***	***C***	***C***
		GMP Compliance & Project Risk Assessment	***C***	***C[1]***	***C***	***C***	***N/A***
2	Define	User Requirement Specification	***C[1]***	***C[1]***	***C***	***C***	***C***
		Study Data					
		Functional Requirements (incl. Manufacturing Data)					
		System Design Requirements					
		Instrumentation Data					
		Requirements Specification Review / Report / Release	***C[1]***	***C[1]***	***C***	***C***	***N/A***
3	Select	Supplier Pre-qualification	***C***	***C***	***C***	***C***	***CS***
		Supplier Evaluation	***C***	***CS***	***C***	***C***	***CS***
		Component Evaluation	***C***	***CS***	***C***	***C***	***CS***
		Supplier Quality Plan (incl. SQAP)	***S***	***CS***	***CS***	***S***	***S***
		Supplier Evaluation Report	***C***	***C***	***C***	***C***	***N/A***
4	Design	Functional Design Specification	***S***	***CS***	***CS***	***S***	***S***
		Hardware Design Specification	***S***	***CS***	***CS***	***S***	***S***
		Software Design Specification	***S***	***CS***	***CS***	***S***	***S***
		Software Module Specification	***S***	***CS***	***CS***	***S***	***S***
		Software Coding Procedure and Record	***S***	***CS***	***CS***	***S***	***N/A***
		Software Description / Flowchart / Pseudocode	***S***	***CS***	***CS***	***S***	***N/A***
		Engineering Standards	***S***	***CS***	***CS***	***S***	***N/A***
		P&I Drawings	***S***	***CS***	***CS***	***S***	***N/A***
		Instrument Schedule	***S***	***CS***	***CS***	***S***	***N/A***

Number	Step	Key Documentation	Prepare	Review	Approve	Maintain	Implement
5	Construct	Software Module Test Specification	***S***	***CS***	***CS***	***S***	***S***
		Hardware Assembly & Test Specification	***S***	***CS***	***CS***	***S***	***S***
		Software Module Integration Test Specification	***S***	***CS***	***CS***	***S***	***S***
		Hardware & Software Test Reports	***S***	***CS***	***CS***	***S***	***N/A***
		Acceptance Test Specifications (System Integration & FAT)	***S***	***CS***	***CS***	***S***	***S***
		Factory Acceptance Test Report	***S***	***CS***	***CS***	***S***	***N/A***
		Instrumentation Inspection Procedure	***S***	***CS***	***CS***	***S***	***S***
		Engineering / Installation Drawings	***S***	***CS***	***CS***	***S***	***S***
		Instrument Specification Sheets	***S***	***CS***	***CS***	***S***	***S***
		Loop Diagrams	***S***	***CS***	***CS***	***S***	***S***
		Equipment / Material Certificates	***S***	***CS***	***CS***	***S***	***N/A***
		System Operating Procedures	***S***	***CS***	***CS***	***S***	***N/A***
		Maintenance Manuals	***S***	***CS***	***CS***	***S***	***N/A***
		Recommended Spares List	***S***	***CS***	***CS***	***S***	***C***
		Design Review / Report / Release*	***C***	***CS***	***C***	***C***	***N/A***
6	Integrate and Install	Instrument Calibration Certificates	***S***	***CS***	***CS***	***S***	***N/A***
		Installation Standards	***S***	***CS***	***CS***	***S***	***S***
		Installation Verification Report	***S***	***CS***	***CS***	***S***	***N/A***
		Site Acceptance Test Specification	***S***	***CS***	***CS***	***S***	***S***
		Site Acceptance Test Report / * Release	***S***	***CS***	***CS***	***S***	***S***
		Project Validation File	***S***	***CS***	***CS***	***S***	***N/A***
7	Qualify	Installation Qualification Protocol	***C[1]***	***C[1]***	***C***	***C***	***C[1]***
		Installation Qualification Summary Report	***C[1]***	***C[1]***	***C***	***C***	***N/A***
		Operational Qualification Protocol	***C[1]***	***C[1]***	***C***	***C***	***C[1]***
		Operational Qualification Summary Report	***C[1]***	***C[1]***	***C***	***C***	***N/A***

Number	Step	Key Documentation	Prepare	Review	Approve	Maintain	Implement
8	Evaluate	Performance Qualification Protocol	***C*[1]**	***C*[1]**	***C***	***C***	***C*[1]**
		Performance Qualification Summary Report	***C*[1]**	***C*[1]**	***C***	***C***	***N/A***
		Deviation Analysis & Corrective Action / Records	***C*[1]**	***C*[1]**	***C***	***C***	***C*[1]**
		Final (Validation) Report / Release	***C***	***C*[1]**	***C***	***C***	***N/A***
		Periodic Review	***C*[1]**	***C*[1]**	***C***	***C***	***C*[1]**
		Performance Monitoring Procedure	***C*[1]**	***C*[1]**	***C***	***C***	***C*[1]**
		Internal Audit / Records	***C*[1]**	***C*[1]**	***C***	***C***	***C***
		System Management Procedures	***C*[1]**	***C*[1]**	***C***	***C*[1]**	***C***
		Operating Procedures	***C*[1]**	***C*[1]**	***C***	***C*[1]**	***C***
		System Security Procedures	***C*[1]**	***C*[1]**	***C***	***C*[1]**	***C***
		Change Control / Records	***C*[1]**	***C*[1]**	***C***	***C***	***C***
		Document Control / Records	***C*[1]**	***C*[1]**	***C***	***C***	***C***
		Configuration Management / Records	***C*[1]**	***C*[1]**	***C***	***C*[1]**	***C***
		Contingency Plans and Disaster Recovery	***C*[1]**	***C*[1]**	***C***	***C*[1]**	***C***
		Maintenance Procedures and Records	***C*[1]**	***C*[1]**	***C***	***C*[1]**	***C***
		Contractor Control	***C*[1]**	***C*[1]**	***C***	***C***	***C***
		Re-validation	***C*[1]**	***C*[1]**	***C***	***C***	***C***
		Decommissioning	***C*[1]**	***C*[1]**	***C***	***C*[1]**	***C*[1]**
		Validation Process Modification	***C***	***C***	***C***	***C***	***C***
		Training Program	***C*[1]**	***C*[1]**	***C***	***C*[1]**	***C*[1]**
		Evaluation Summary Report	***C*[1]**	***C*[1]**	***C***	***C***	***N/A***
		Validation File	***C*[1]**	***C*[1]**	***C***	***C***	***N/A***

Key:

C = CLIENT
S = Siemens as SI
***C*[1]** = SIEMENS can assist as a value-added service, and as contracted.
N/A = NOT APPLICABLE

Notes:
SOPs will be needed for preparation and implementation of procedures, reviews, approvals. These SOPs may be „generic„ or task specific.
Many activities are on-going throughout the computerized system life-cycle and validation documentation will need to be updated accordingly.

APPENDIX NO. 3 MANUFACTURING DATA SPECIFICATION

Structure / Content

Introduction

- Document author(s), authority, scope and purpose
- Manufacturing processes covered
- Contractual status
- Relationship with other documents (e.g. Front End Study, URS, Project and Quality Plan)
- GMP and Validation requirements
- Environmental requirements
- Hazardous Area Classification

Operations Overview

This section should summarize the manufacturing process which is to be automated and include, as applicable:

- Product list, i.e. number of products to be produced
- Physical properties of materials and ingredients used
- Product recipe, defining the recipes for each product by:
  - Formula and materials used
  - Procedure for manufacture
  - Equipment units and their boundaries
  - List of unit operations and their definitions
  - List of process phases
- Any special operating requirements
- A process flow diagram from which all the process measurements and control devices can be identified, along with any interactions
- Alarms, hard wired trips and fail safe modes for all instrument protective systems complete with a detailed description of the method of operation and conditions for reset etc.
- Operator interface (central / remote)

Application Engineering Data

This section should define each process parameter that may :

- Be measured or controlled
- Compromise the quality of the product (Critical Process Data)
- Give rise to abnormal conditions
- Require safety interlocks and / or alarm monitoring

It is recommended that Critical Process Data be highlighted and also listed separately to enable easy identification and control.

For each process parameter, the following should be defined:

Method of cross referencing to one or more of the following:

- The Tag No. of the instrument to which it applies
- Process flow diagram
- Equipment or line identification
- Operating procedures

Units of measurement

Data point tolerance

Working ranges and limits for process instrumentation and modulating valves

Minimum and Maximum values that line instruments can be exposed to

Data Recording

For data recording this should state which measurements and data are required to be collected for transmission to other systems, and the required frequency and method of data recording within and external to the system.

Testing Requirements Overview

This section should outline how the computerized system is to tested at Design Qualification, installation Qualification, Operational qualification , Performance qualification and throughout its operational life to ensure conformance with the requirements of the Manufacturing Data Specification.

Consideration should be given to the method of validating data, including:

- Reviews of algorithms
- Testing across full operating ranges
- Testing at the range boundaries
- Testing of automatic process sequence operation
- Testing of alarms and hard wired trips
- Verification of data acquisition, recording, retrieval and networking
- The need for specific test data, conditions or equipment
- Recording of test results

APPENDIX NO. 4 REQUIREMENTS SPECIFICATION :

APPENDIX NO. 4A REQUIREMENTS OUTLINE

Information to consider for System Requirements:

I Functional Requirements

A. Purpose of System
a) Overall system description
b) Clear statement of what the system is to do
c) Expected benefits
d) Relation to other systems

B. Description of Controlled Function
a) Description of operation
b) Control philosophy
c) Description of cycles

C. Information Input
a) Measured inputs
b) Discrete inputs
c) Operator inputs
d) Input from other systems
e) Data input verification

D. Material Input
a) Manual loading
b) Automatic loading
c) Input from other systems
d) Checks on material input

E. Recipe Management
a) Definition
b) Verification
c) Loading
d) Security

F. Data Processing
a) Input data conversions
b) Calculations
c) Validity checks
d) Control strategies and algorithms

G. Control Output
   a) Analog
   b) Discrete
   c) Alarms
   d) Operational interlocks
   e) Start-up states
   f) Power failure recovery

H. Information Output
   a) Status
   b) Events
   c) Alarms
   d) Displays
   e) Reports
   f) Data archiving
   g) Output to other systems

I. Operating Modes
   a) Automatic modes
   b) Manual operation
   c) Maintenance mode
   d) Operational interlocks

J. Alarm Management
   a) Action
   b) Priority
   c) Reporting
   d) Acknowledgment
   e) Power failure

K. Security
   a) Levels
   b) Means of access
   c) Parameter modification
   d) Program access

L. Analog Data Update Time
   a) Control outputs
   b) Alarms
   c) Displays
   d) Reports
   e) Archived data
   f) Transmission to other systems

M. Discrete Data Update Time
- a) Control outputs
- b) Alarms
- c) Displays
- d) Reports
- e) Archived data
- f) Transmission to other systems

N. Response to Operator Inputs
- a) Analog
- b) Discrete
- c) Alarm

II Physical Requirements

A. System Structure
- a) Layout of components
- b) Relation to facilities and other systems

B. Size restrictions

C. Materials
- a) Type
- b) Finishes

D. Utilities
- a) Electrical
- b) Water
- c) Steam
- d) Air

E. Environmental
- a) Temperature
- b) Vibration
- c) Electrical interference
- d) Humidity

APPENDIX NO. 4 REQUIREMENTS SPECIFICATION :

APPENDIX NO. 4B URS STRUCTURE

Structure of the User Requirements Specification

The URS can contain a large number of requirements. It should therefore be structured in a way that will permit easy access to this information. A means of referencing items such as chapters, lists, tables, figures and each requirement will be necessary, particularly if the Functional Design Specification is to be cross-referenced to the URS.

A number of general guidelines apply:

- Requirements should be defined precisely. Vague statements should never be used. The scope for readers to make assumptions or misinterpret should be minimized.
- Each requirement statement should have a unique reference.
- Requirement statements should be expressed in terms of. functionality and not in terms of design solutions or ways of implementing the functionality.
- Each requirement statement should be testable. This is particularly important for computerized systems subject to validation because Performance Qualification (PQ) testing is normally carried out against the URS.
- The URS must be understood by both client representatives and suppliers. The use of diagrams is often useful.
- Where applicable, mandatory requirements and desirable features should be distinguished.

The final responsibility of defining system requirements rests with the pharmaceutical manufacturer. However, prospective suppliers can be requested by the URS to supply as part of their quotation, information on how issues are to be addressed satisfactorily. Such issues could include:

- data integrity
- data storage / retrieval
- access security system availability
- threats assessment
- training
- source code availability

It is suggested that the URS is structured as below:

Introduction

1. System Overview

2. Manufacturing Data
   - Operations Data
   - Application Engineering Data

3. Operational Requirements
   - System Functions
   - System Modes of Operation
   - System Equipment
   - System Data and Timing
   - System Availability
   - Safety
   - Access Security
   - Data Integrity
   - Data Storage / Archiving / Retrieval
   - Diagnostics

4. System Networks / Interfaces
   - Measurement and control Instrumentation
   - Other Systems
   - Graphical User Interface

5. System Environment

6. Inspection / Acceptance Testing

7. Quality and Validation Procedural Requirements

8. Documentation

9. System Development and Support Requirements
   - Compatibility and Enhancement Potential
   - Maintainability
   - Training
   - Life-cycle
   - System Support Agreements
   - Resource

10. Delivery and Installation

11. Commercial Considerations

12. Terminology

The above structure ensures that all major topics are covered by the URS. However it is recognized that the URS author needs the ability to structure the information in a manner most appropriate to the system in question. For example:

- System generated reports may be defined as part of *System Functions* rather than under *System Interfaces.*

- Data could be sensibly defined under *System Functions, System Data and Timing* or *System Interfaces.*

- *System Modes of Operation* could be combined with *System Functions.*

It is important that the URS author treats this outline structured as a guide to be applied appropriately. Considerations to bear in mind when structuring the URS include:

- Determining the critical (core) functions of the system.

- Determining whether the scope of the URS covers any connected equipment or whether this is defined elsewhere (e.g. measurement and control instrumentation which may be supplied under separate contract).

- Determining whether the URS is to be used as an outline document during a Front End Study or whether it is to be used as a basis for formal quotation by suppliers.

- Determining whether the URS is to define the requirements for a complete system, or whether it is to define *system type* or *application specific* requirements.

APPENDIX NO. 5 REQUIREMENTS SPECIFICATION REVIEW

A Requirements Specification Review Team is normally made up of relevant project and maintenance engineering disciplines and representatives from Quality , Validation and Owner Departments.

Documents to be reviewed would include:

- Front End Study
- Manufacturing Data Specification
- Critical Process Data
- Test Criteria
- User Requirement Specification
- Validation Project Plan
- Validation Document Matrix
- Project and Quality Plan
- GMP Compliance / Validation Project Risk Analysis
- Supplier Audit Reports
- Inquiry Package Documentation

The requirements specification document review can be conducted using the following checklists:

- Technical Checklist, which covers:
  - operational \ system requirements
  - data specification
  - networks
  - interfaces

- Quality Checklists, which covers the following issues:
  - general quality
  - validation (regulatory)
  - working methods / procedures
  - availability
  - maintainability
  - environment
  - safety
  - security

- Commercial Checklist
  - contractual responsibilities
  - program requirements
  - resourcing

The use of such checklists will help ensure that all important issues have been addressed and documented. Likewise the review team should use the checklists to ensure that requirements are not duplicated, possibly causing ambiguity.

The prospective suppliers of the process control system should be reviewed as part of the requirements specification qualification exercise in order to obtain assurance that the component was initially developed using quality development methodology. The more effort put in by the supplier in order to provide assurance that the system will perform as intended, the less work that will need to be performed by the client as part of the validation process to qualify the computerized system.

The intended contract with the supplier should be reviewed to ensure that it clearly describes the responsibilities of the supplier and of the client for supporting the computerized system.

The Requirement Specification Review should be documented, indicating the actions taken during the review and including any supporting documentation to ensure and demonstrate that the controls required to specify the design have been addressed and agreed by the Client, and where appropriate the in house implementation group.

On completion a Review Report will be produced and which should contain the following information:

- Who was involved in the Specification review process.
- Any Checklists used
- What actions arose from the review process
- How the actions have been progressed and closed off.
- The documents that make up the qualified set.
- When was a Specification Qualification Certificate granted (with any
- associated reservations)

The review meeting report should also include a schedule itemizing any documentation which requires updating and those responsible for completing the work. Changes must be carried out under a change control procedure prior to issue for quotation.

The supplier selection exercise may progress provided review and approval of any new or revised information is undertaken. The Design Phase should not be undertaken until the Requirements Specification Review certificate has been signed by nominated personnel.

A review of the GMP Compliance / Validation Project Risk Analysis should undertaken at this time and included as a section in the Requirement Specification Review Report.

The Specification Review Report should be retained in the Project Validation File for future reference.

APPENDIX NO. 6: SYSTEM INTEGRATOR QUALITY PLAN STRUCTURE

Overview

A Quality Plan should be produced by the System Integrator and the Component Manufacturer as the first deliverable during the Design Phase. The Component Manufacturer's Quality Plan will focus on the pertinent quality elements related to the design, development, marketing and support of components for commercial application. Subsequent applications would be developed by the System Integrator in accordance with a defined methodology and a Project Quality Plan jointly approved by the client and System Integrator.

In each case, the Quality Plan defines the detailed quality procedures to be followed by the supplier. In the case of the System Integrator, it will usually reference the high level Project and Quality Plan which is typically produced by the pharmaceutical manufacturer during the Planning and Definition Phases.

The Project Quality Plan may be revised at various points in the project. Such revision should be agreed with the client and approved by the appropriate authority and be subject to change control.

The System Integrator is responsible for providing and adhering to the Project Quality Plan.

Purpose

The purpose of the Project Quality Plan is to define the quality management system and activities which the supplier intends to use to assure the achievement of the required quality on the project.

It is a contractual document and should be jointly approved by the client and System Integrator. It should be adequate to ensure that:

- Quality Management System requirements are met at all stages of the project.
- The finished component and documentation will meet quality requirements.
- Project timescales and budgets will be met.

It should be easily understood by the client project team members, System Integrator project team members, and any third parties e.g. auditors or inspectors.

It should clearly fulfill external regulatory and/or contractual requirements.

When approved, the Project Quality Plan will be the reference document for all verification activities such as audits and reviews carried out on deliverables defined in the System Integrator scope of supply.

The Project Quality Plan needs to be a high profile documented procedure and it must communicate this information to all client project team members, System Integrator representatives or third party suppliers as appropriate.

Outline of a Project Quality Plan

There is no mandatory format for a Project Quality Plan. However, the outline given below can be used to check if all necessary areas have been covered.

A Project Quality Plan should reference, as appropriate:

- System Integrator Procedures and Standards
- Project-Specific Procedures and Standards Software Quality Assurance Plan
- Purchaser Procedures and Standards, as specified in the contract

Though details of the Project Quality Plan differ somewhat from those typical of a client's Quality Plan, the primary components are similar. It should also be noted that details of the Quality Plans for the System Integrator and Component Manufacturer will also differ as appropriate to suit their respective business objectives. However, each should contain the following or equivalent:

- Introduction
  Documentation Control
  Project Overview and Scope
- Organization
  - Quality System
  - Structure
  - Responsibilities
- Design / Construct Plan
  - Validation Phases and Verification
  - Project Plan / Task Schedule
  - Progress Control
- Quality Standards and Objectives
  - Configuration Management
  - Change Control
  - Deviation Recording and Corrective Action
  - Techniques and Methodologies
  - Sub - Contractor Control
  - Purchasing Controls
- Documentation and Software Production Tools
- Appendices
  - Detailed project plan
  - Approval matrix
  - Project and Quality Plan activity schedule

APPENDIX NO. 7 FUNCTIONAL DESIGN SPECIFICATION

APPENDIX NO. 7A SPECIFICATION CONSIDERATIONS

I Controlled Function

A. Operating Modes
   a) Automatic mode
   b) Manual mode
   c) Maintenance mode
   d) Operational interlocks

B. Description of Operation
   a) Sequence of operation
   b) Modifiable parameters
   c) Limiting conditions

C. Controlled Elements
   a) Valves, heaters, motors . . .
   b) I\P, relays, solenoids, motor starters . . .

II Computer System

A. Hardware
   a) CPU
   b) Memory devices
   c) Recording devices
   d) Communication interfaces
   e) Operator terminals

B. Software
   a) Operating system
   b) Communication drivers
   c) Network controllers
   d) Configurable programs
   e) Application programs

III Information Input

A. Measured inputs
   a) Number, type, and location of each sensor
   b) Type, model number, and software version of all transducers and signal converters
   c) Model number and software version of all analog input modules
   d) Tag name, location, data type, and valid range of all analog inputs

B. Discrete inputs
   a) Type, model number, and software version of all discrete input modules
   b) Tag name and location of all discrete inputs

C. Operator inputs
   a) Entry and verification means
   b) Entry modes
   c) Error detection
   d) Error correction
   e) Tag name, description, and range of parameters
   f) Electronic signatures

D. Recipe inputs
   a) Definition
   b) Loading
   c) Verification
   d) Security
   e) Tag name, description, and range of parameters
   f) Electronic signatures

E. Input from other systems
   a) Source
   b) Communication mode
   c) Error detection
   d) Error correction
   e) Tag name, description, and range of parameters

IV Material Input

A. Loading
   a) Manual loading
   b) Automatic loading
   c) Input from other systems

B. Checks on material input

V Data Processing

A. Input data
   a) Data conversions
   b) Scaling
   c) Calibration means
   d) Error detection and correction

B. Calculations
   a) Tag names of input parameters
   b) Algorithms
   c) Control strategies
   d) Tag names and ranges of output parameters
   e) Error detection and correction

VI Information Output

A. Control
   a) Tag name, location, range, and default value of analog outputs
   b) Model number, software version, and location of each analog output module
   c) Type, model number, software version, and location of each output driver

B. Alarms
   a) Tag name, type, and location of alarm outputs
   b) Type and location of alarm indicator
   c) Acknowledgment means

C. Displays
   a) Tag name of data values
   b) Tag name of status indicators
   c) Event indication
   d) Alarm indication

D. Printed Reports
   a) Tag name of data values
   b) Tag name of status indicators
   c) Event recording
   d) Alarm recording
   e) Report generation

E. Transmission to other systems
   a) Tag names of data values
   b) Tag names of status indicators
   c) Event transmission
   d) Alarm transmission
   e) Report transmission
   f) External request of data

F. Archived data
   a) Tag name of data values
   b) Tag name of status indicators
   c) Event recording
   d) Alarm recording
   e) Report generation
   f) Audit trail

VII Operational Features

A. Alarm Management
   a) Action
   b) Priority Reporting
   d) Acknowledgment
   e) Power failure

B. Security
   a) Levels
   b) Means of access
   c) Parameter modification
   d) Program access

C. Safety
   a) Physical interlocks
   b) Software interlocks
   c) Emergency shut-down and recovery

D. System Failure
   a) Failure modes
   b) Default state
   c) Recovery modes

E. Analog Data Update Time
   a) Control outputs
   b) Alarms
   c) Displays
   d) Reports
   e) Archived data
   f) Transmission to other systems

F. Discrete Data Update Time
   a) Control outputs
   b) Alarms
   c) Displays
   d) Reports
   e) Archived data
   f) Transmission to other systems

G. Response to Operator Inputs
   a) Analog
   b) Discrete
   c) Alarm

APPENDIX NO. 7 FUNCTIONAL DESIGN SPECIFICATION :

APPENDIX NO. 7B FDS STRUCTURE

The structure of the Functional Design Specification should parallel that of the User Requirement Specification, in order to facilitate the cross checking of the two documents. A cross reference should be included in the FDS indicating the degree of compliance with the URS. This cross reference may be included as an appendix to the FDS.

The FDS should be structured in a way that will permit easy access to information. A means of referencing items such as chapters, lists, tables and figures may be necessary, particularly since the Functional Design Specification should be cross-referenced to the System Acceptance Test Specification.

A number of general guidelines apply:

- Vague or ambiguous statements should be avoided. The scope for readers to make assumptions or misinterpret should be minimized.
- Each function should have a unique reference.
- Specification of functionality should not be duplicated.
- Each function defined should be testable. This is particularly important for systems subject to validation because Factory and Site Acceptance Testing is carried out against the FDS.
- The FDS should be understood by both the client's representatives and suppliers; jargon should therefore be avoided. The use of diagrams is particularly useful.

A suggested structure for the FDS is as follows:

1. Introduction
2. System Overview
3. Manufacturing Data
4. Operational Functions
    - System Functions
    - System Modes of Operation
    - System Equipment
    - System Data and Timing
    - System Availability
    - Safety
    - Access Security
    - Data Integrity
    - Data Storage / Archiving / Retrieval
    - Diagnostics

5. System Networks / Interfaces
   - Measurement and control Instrumentation
   - Other Systems
   - System Operators
6. System Environment
7. Testing
8. Quality and Validation Procedural Characteristics
9. Documentation
10. System Development and Support
    - Compatibility and Enhancement Potential
    - Maintainability
    - Training
    - Life-cycle
    - System Support Agreements
11. Delivery and Installation
12. Commercial Considerations
13. Terminology

If the process control computer supplier is also contracted to specify, design, test and install the measurement and control instrumentation, then these important elements of the computerized system must be application engineered, fully documented and integrated under the same validation methodology to the project life-cycle.

The above structure ensures that all major topics are covered by the FDS. However it is recognized that the FDS needs to be structured in a manner most appropriate to the system and application in question.

APPENDIX NO. 8 DESIGN REVIEW

Overview

The pharmaceutical manufacturer must ensure the design has been documented, and that the design meets the specified requirements. The quality of the supplier's implementation of the design has to be checked. The pharmaceutical manufacturer have to demonstrate that all computer systems used in the production of licensed components will consistently perform as specified. Important evidence of this is the ability to:

- Show how the design meets the specification (user requirements).
- Prove that the design has been implemented professionally, in accordance with accepted industry best practice.

In addition, it is particularly important for the client that the flexibility and maintainability of the design, and how the design meets the specified requirements, is understood. These are issues which, if not built into the design, can lead to considerable problems and cost after system hand-over to the pharmaceutical manufacturer (i.e. during the maintenance phase).

To conduct a Design Review the following need to be addressed:

- Responsibilities
- Supplier Project Group
- Ensures that a Design Qualification is carried out in accordance with the relevant procedures.
- Ensures that all actions arising from the Design Review are progressed and completed satisfactorily.
- Provide all documentation and information necessary to undertake the review.
- Client Group
- Ensure correct Client representation on Design Review team to review design and construct phase activities and documentation.
- Secures ratification of qualification exercise by Quality assurance.

Purpose / Scope

The purpose of the Design Review is to ensure that all supplier design and associated documentation has been reviewed and verified that it meets the agreed plans and pharmaceutical manufacturer's requirements. It is a complete technical and quality review of all design activities, which comprise:

The final computer system design, which is made up of hardware and software documentation. This design should be checked for compliance against:

- The User Requirements Specification
- The Manufacturing Data Specification (including critical process data)
- The Functional Design Specification
- The Validation Project Plan
- The Project and Quality Plan

The implementation and integration of the computer system design, which should be checked for compliance against all life-cycle documentation and activities, including:

- The Functional Design Specification
- The Software Design Specification
- The Software Module Design Specifications
- The Hardware Design Specification
- The Hardware Test Specification
- The Software Module Test Specifications
- The Software Module Integration Test Specification
- The Acceptance Test Specification
- Software Production Methodology and Walkthroughs
- The Supplier Quality Plan (including the SQAP)
- The Project and Quality Plan

The application engineering activities, which are documented by instrument, electrical, mechanical and process engineering drawings, specifications and data sheets. This design should be checked for compliance against:

- The Manufacturing Data Specification, including critical process data
- The Measurement and control Instrumentation Application Specifications
- The Validation Project Plan
- The Supplier Quality Plan
- The Project and Quality Plan

- The factory construction and calibration of the measurement and control instrumentation, which should be checked for compliance against:
  - The instrument, electrical, mechanical and process engineering drawings, specifications and data sheets.
  - The Supplier Quality Plan
  - The Project and Quality Plan

- Standard documentation supplied, such as:

  - System reference manuals
  - System Maintenance Manuals
  - System Hardware Specifications
  - Manufacturers Specification Sheets for instruments

Design Review Team

Design Review can comprise of one or a number of review meetings, arranged by the supplier project manager. The project manager should ensure that all relevant disciplines are represented during the review process, which will typically include the following:

- All members of the validation team and project team (if different).
- Operational management and personnel.
- Maintenance personnel.
- Key personnel from the validation consultancy (as applicable).
- Key personnel from the supplier.

Design Review is the responsibility of the pharmaceutical manufacturer and it would be advantageous to utilize the continuity and job-knowledge of members the Specification Qualification team. It is the System Integrator's responsibility to provide all documentation and information necessary for the client to undertake the review.

Design Qualification Documents

The following documents would typically be reviewed during the Design Qualification:

- Requirements Specification Review documentation.

Supplier Quality Plan

- Functional Design Specification

- Software Design and Test Specifications
- Software Test Results / Report

Hardware Design and Test Specifications

- Hardware Test Results / Reports
- Flow Diagrams
- System Diagrams (including network diagrams** and data communication standards)
- System Manuals
- System Manager Manuals
- Material and Equipment Lists
- Instrument Application Specifications
- Engineering Drawings
- Application source code (or evidence of code walk-throughs)
- A listing of any deviations from the URS for the system developed.
- Compliance Matrix (List of functions with reference to their quality critical nature)
- Change Control Records
- Calibration certificates
- Factory Acceptance Test Specifications
- Factory Acceptance Test Results

(** Network documentation identifying / referencing Network Operating Software, Transport Protocols and physical components e.g. cables, clients, servers of the Data Link and Physical layers.)

Review Process

The supplier project manager should assess each document in the design package and should decide:

- The scope of the review to be undertaken
- The most appropriate personnel to conduct the review.

Each review meeting should be recorded and such minutes should contain the following information as appropriate:

- Reference, number and version of documents reviewed.
- Agreed changes to documents.
- Other comments from the reviewers with agreed actions as necessary.

The various documents should be scrutinized against the following checklists:

- Software Design Checklist, which covers the following issues:
  - Software design, including support documentation .
  - Software Coding.
- Hardware Design Checklist.
- Instrumentation Checklist.
- Operations Data Checklist.
- General Design Checklist, which covers the following issues:
  - Availability.
  - Maintainability.
  - Compatibility and Enhancement Potential.
  - Environment.
  - Safety.
  - Security.
- Quality Checklist.
  - Documentation
- Commercial Checklist.
  - contractual responsibilities
  - program requirements
  - resourcing review

The use of these checklists will help ensure that all important issues have been addressed, and that the design meets the specified requirements.

Design Review Report

The supplier project manager should be responsible for producing a Design Review Report, which contains the following information:

- Who has been involved in the design qualification process.
- Any checklists used.
- What actions arose from the qualification process.
- How the actions have been progressed and closed off.
- The documents which make up the qualified documentation set.

When was a Design Review Certificate granted (with any associated reservations)?

All of the above may have been documented in the review meeting minutes, in which case the minutes will form the Design Review Report.

The Design Review meeting report should also include a schedule itemizing any remaining documentation which requires updating and those responsible for completing this work. The progress of updates should be monitored through the documentation management system against agreed completion dates. All updates should be completed before delivery to site.

A review of the GMP Compliance / Validation Project Risk Analysis should undertaken at this time and included as a section in the Design Review Report.

Design Review Release Certificate

The Design Review meeting should decide whether the outstanding actions prevent the issue of a release certificate. If so, the meeting should agree another review date to accept the changes and issue the certificate. Otherwise a Design Review Release Certificate should be completed and approved by designated members of the validation team. The meeting minutes should document whether or not a certificate was granted (and if granted with reservations, the number and nature of those reservations should be noted).

The release certificate and report should be retained in the Project Validation File for future reference.

The Qualification Phase should not be undertaken until the Design Review certificate has been signed by nominated personnel and satisfactory completion of the Install and Integrate Step activities, testing and acceptance.

APPENDIX NO. 9 QUALIFICATION PROTOCOLS

Purpose

This guideline is intended to identify and outline the qualification activities, tasks and testing to be performed when qualifying Process Control Systems (Computerized Systems).

Objective

The guideline introduces the concept of identifying computerized system qualification activities in the form of Computer Installation Qualification (CIQ), Computer Operational Qualification (COQ), and Performance Qualification (PQ).

The activities related to this guideline that need to be implemented include the following:

Preparation of Qualification Protocols (CIQ/COQ/PQ)
Preparation of standard procedures used to implement the protocol.
Execution of Qualification Testing (as defined in the Qualification Protocols)
Identify all standard operating procedures required for use in operating the Computerized System in its Operating Environment.

Scope

This guideline applies to the qualification (CIQ/COQ/PQ) of the following systems:

Automation Level 1 Programmable Logic Controllers (PLCs) used to control equipment and systems.

Automation Level 2 Process Control Systems used for supervisory process control and management, data acquisition, and operator interface.

The qualification activities and tests listed in this Guideline have been defined in terms of separate CIQ, COQ and PQ Protocols. However, in many cases it may be preferable to include the CIQ and COQ testing as part of the equipment/system IQ and OQ Protocols, respectively. This determination to be agreed by the client and supplier and based on the scope (deliverables) of the project as defined in the contract and / or the technical merit of the chosen approach.

The guideline provides the framework for the procedures to be followed in qualifying computerized systems and descriptions of the activities and tasks that shall be performed throughout all stages of the qualification process for newly installed process control systems. Development of detailed procedures is the function of validation procedures.

Guidance is also provided on the general tests to be performed for Computer Installation Qualification (CIQ), Computer Operation Qualification (COQ), and Performance Qualification (PQ).

The scope of the CIQ Protocols shall include equipment controllers (PLCs), Operator System workstation PCs, and the network server with interface database. Each CIQ Protocol shall be designed to be consistent with the computer system's control strategy and configuration, and shall be based on a nodal approach. Workstations interfaced with several equipment PLCs may be qualified under a dedicated CIQ Protocol for the workstation, or may be qualified as part of the equipment CIQ. Wherever possible, workstation PCs shall be qualified as part of the equipment/system CIQs. A separate CIQ shall be conducted for the system network server with interface database.

The scope of the COQ Protocols shall include equipment controllers (PLCs) and workstation PCs. Testing shall be conducted to verify proper data transfer and data integrity from the workstation to and from the equipment PLCs and operator interface between the workstation and equipment/system. Each COQ Protocol shall be designed to be consistent with the computer system's control strategy and configuration, and shall be based on a nodal approach. Workstations interfaced with several equipment PLCs shall be qualified under individual COQ Protocols for each piece of equipment. Equipment PLCs interfaced with several workstations shall be qualified under a single COQ Protocol. COQ testing results, where applicable, shall be recorded and printed from the computer system to indicate actual transfer data operator interface real-time results.

The scope of the PQ Protocol, shall focus on information or data which is being exchanged between the workstations process database, network server, and interface database. Qualification issues and activities to be addressed are outlined in the following sections.

Guideline-In-Practice

Key validation documentation from the pharmaceutical manufacturer and the process control system supplier shall be reviewed for a general understanding of the system. This documentation must also be reviewed in order to ensure that it is sufficient to begin Qualification Protocol preparation (CIQ/COQ/PQ). Documentation required to determine Qualification Protocol preparation includes but is not limited to:

- Validation Plan(s)
- Quality Plan(s)
- Compliance and Risk Assessment
- Inventory Control Procedure
- Change Control Records
- Document Control Procedure

- SOP status listing
- User Requirement Specification (including Manufacturing Data)
- Functional Design Specification
- Design Review Report
- Complete and accurate Pipe and Instrumentation Diagrams (P&IDs).
- A complete annotated input/output (I/O) listing, along with an application source code cross-reference.
- A complete and fully commented copy of the application source code in hard copy form (electronic copies of the source code may also be required).
- A system architecture diagram, along with a complete component listing of measurement and control instrumentation, plus any components supplied by others as part of the computerized system and not identified on the architecture diagrams.
- A description of operations which describes all modes of operation (e.g., start-up, shutdown, manual/automatic), indicating all alarms with limits, actions, and responses.
- A complete and accurate listing of each process graphics screen for each workstation which includes all I/O points being displayed.
- Any specific requirements for the system which have been defined by the client.

Note: Complete and accurate system specification documentation is needed to enable detailed development of Qualification Protocols.

Qualification : Verifications and Tests

Computer Installation Qualification (CIQ) Preparation

CIQ protocols shall be developed to verify and document that all critical aspects of a process control computer control system have been installed in accordance with the approved system design specifications, manufacturer's installation specifications, and as-built drawings and documentation.

CIQ verifications for the system shall include the following verifications and tests:

- Computer System Installation Description
  - Architecture
  - Number and type of nodes
  - Network(s)
  - Communication protocol(s)
  - Hardware components
  - Number of I/O
  - Software Package
  - Operating system
  - Drivers
  - I/O
  - Usage/Functionality
  - Operator interface
  - Data acquisition
  - Data archiving
  - Alarm management
  - Reports
  - Supervisory control
  - Systems integration / interface (e.g., MES, LIMS)

- Computer System Project File Verification

A verification of the Process Control System's project validation file for all relevant validation documentation shall be performed to ensure that the system is adequately documented to assure compliance with the Validation Project Plan and that:

- This documentation is under appropriate document control and traceability among the documents has been maintained (see 3.6.3).
- That all documents in the file are current and reflect the as-built system.
- All documents required for the validation project file are in the file.
- Deviations from the Validation Project Plan have been documented, and appropriate analysis, recommendations and actions have been recorded.

This verification shall be conducted for three (3) main categories of documentation:

- Essential Documentation: Documentation which must be present and on-file before executing the CIQ Protocol for the system.

- Required Documentation: Documentation which must be present and on-file in order to adequately document the system.

- Informational Documentation: Documentation which provides additional information about the system but which is not essential to the execution of the CIQ Protocol or required to adequately document the system.

Essential documentation includes (but is not limited to) the following:

- Final As-built Drawings including:
- Electrical drawings to include I/O wiring diagrams
- System cabling diagrams
- System/hardware architecture diagrams
- Hardware and Software Manuals (to include but not be limited to)
- Process Control System (I/O modules, CPU, etc.)
- Process Control System (programming, database, security, setup and configuration etc.)
- Network (adapters, i.e., token ring)
- Design Review Report

Required documentation includes (but is not limited to) the following:

- Approved System Specifications
- Annotated hard copy of the application source code [process control system]
- Backup software (to include but not be limited to)
- Current operating system
- Process Control System programs/files
- Process Control System I/O driver software
- Comments and symbols for application files
- Network interface software (SQL)
- SQL tools
- Draft SOPs for Operation, Security, Backup, Data Archiving
- Spare parts listing for hardware components

Informational documentation (as described above) to be identified and reviewed to enable appropriate segregation and control of key validation documents and records.

- Verification of As-Built Documentation

Approved as-built diagrams will be verified to ensure that they adequately and accurately represent the installed computer system. At a minimum, approved as-built diagrams for each system must include the following:

- Process Control System Workstation

As-built system architecture diagrams indicating all hardware components (CPUs, I/O modules, power supplies, modems, PCs, etc.)

As-built system wiring and cabling diagrams indicating all I/O wiring and cabling to the process control system workstations. Wire and cable numbers, types, and termination must also be indicated.

Network Server with Interface Database (as applicable)

As-built system architecture diagrams for the network server indicating all hardware components (hard drive, etc.)

As-built cabling diagrams indicating all network connections between process control system nodes and the network server. Cable numbers, types, and termination must also be indicated.

- Field Connections

As-built wiring / cabling connections to field measurement and control instrumentation, identifying marshalling cabinets / terminations, remote field mounted cabinets / terminations and the instrument tag numbers.

The as-built documentation (diagrams) shall be compared against the installed computer systems. The verified as-built documentation (diagrams) shall be marked up in red to indicate any discrepancies (if identified), and shall be attached to the executed CIQ protocol appendices in order to document this verification.

- Hardware Component Installation Verification

System components (listed below) shall be verified for proper installation location, component type, and other critical information specified for each component. When specified items or parameters cannot be visually verified, the components shall be verified through cross-referencing the recorded manufacturer names and model numbers with manufacturer/supplier documentation (cut sheets) or manuals. The cut sheets or manuals utilized to verify critical components shall be attached to the executed CIQ protocol.

The items to be verified include (but are not limited to) the following:

- Process Control System Workstations/Network File Server

– Personal Computer
– Central Processing Unit (CPU) (e.g., 80486, Pentium, Power PC)
– Hard drive storage capacity (e.g., KB, MB, GB)
– CPU Memory
– Expanded vs. extended, synchronous vs. dynamic
– Keyboards and other peripherals (installation only)
– Mouse
– External storage devices
– Tape drive
– CD
– Graphic and video cards
– Monitors
– Bar-code scanners
– Printers
– Communication modules
– Process control system networks and other LAN cards
– Other cards
– Modem (internal PC or external, including any dedicated phone lines)

- Computerized System Components
– CPU
– I/O modules
– Interface modules
– Rack to rack
– Process Control System to operator interface
– Scale
– Bar-code reader/scanner
– Communication Modules
– Process Control System network (e.g., Data Highway)
– Power supply modules
– Printers
– Racks/Chassis
– All critical field instrumentation (as applicable to contract)

- Power and Circuit Protection

An inspection of the installed power supplies and circuit protection devices to the computer systems shall be performed to ensure that they are properly installed and sized as defined in the manufacturer's manuals. The items to be inspected include (but are not limited to) the following:

– Rack power supplies
– I/O module power fuses
– Circuit breakers to control cabinets
– External fuses to CPU
– Non-interruptible Power Supplies (UPS)

Note: Power in the facility is considered as installed to the respective regulations and that all power distribution is in accordance with all local and national codes. Therefore, the measurement of voltage, current, wave length, and proper grounding is not be considered within the scope of the computerized system qualification. It is recognized however that the correct installation and operation of this utility will need to be confirmed by the pharmaceutical manufacturer and documented as such in the project validation file.

- Hardware Configuration Verification

A visual inspection of the critical computer system hardware shall be performed to document and verify that DIP switch and jumper settings are correctly configured based on the manufacturer's specifications for the specified application. The items to be inspected include (but are not limited to) the following:

– Process Control System CPU
– I/O modules
– Power supplies, racks/chassis
– Printers
– Communication modules

- Interface modules
- Modems
- Bar-code printers and scanners

- System Software Backup

Before beginning the execution of the COQ, a backup of the computer system's Application Programs (source code) and the Workstation configured software, and archived data and network server shall be performed, submitted to the pharmaceutical manufacturer and maintained as the actual backup copies. The backup copies of the programs and files shall be scanned for viruses using the most current supplier or client-supplied virus detection utility. A printout of the executed scan shall be attached to the executed CIQ along with a complete listing of all programs and files in order to verify that all files have been successfully scanned and no viruses were detected.

- Software Installation Verification

Verification shall be conducted for all software for the application or required by the application.

Verifications will include:
- Manufacturer/Supplier
- Version No./Release/Level

Operating System, examples include:
- DOS
- Windows, with all required applications
- Windows NT
- S7 - CPU firmware

Commercial Off-the-Shelf Software (COTS), examples include:
- Microsoft Excel
- SAP

- Software Configuration Verification

Testing shall be conducted to document the software variables of the process control system workstations. The parameters which will be documented or verified include (but are not limited to) the following:

Computerized System

Print out CPU configuration and attach to protocol
Print out I/O module configuration and attach to protocol
Verify I/O scaling values (HI/LO/EGU)
Compare I/O module configuration printout of scaling values to calibration data sheets for I/O devices.

The verification of I/O scaling values will be conducted under display data testing as part of operator interface testing.

Testing shall be conducted to ensure that the software configuration is identical to that specified in the system specifications. Print out or document the system configuration and attach it to the executed IQ Protocol.

Process control system Workstations/Nodes

Print out process control system software configuration and attach to protocol
Print out the PC configuration files:

- CONFIG.SYS (DOS)
- AUTOEXEC.BAT (DOS)
- WIN.INI (WINDOWS)

Check the configuration of network access points and that data access authorities are assigned.

Check that network applications are correctly configured for the network.

Process control system I/O Driver Configuration

Print out process control system software driver configuration and attach to protocol
Channel Communication Settings
- Baud Rate

Device Definitions
- Device name
- Hardware

Poll Record
- I/O address (start, end, length)
- Block configuration (data type, poll time)

General System Inspection

A general inspection of the installed computer systems shall be conducted. The items to be inspected will be listed in the CIQ protocol and shall include (but not be limited to) the following:

- General cleanliness of process control system cabinets
- Disconnected wiring/cables
- Disconnected/broken modules or components
- Disconnected/broken keyboards and other peripherals
- Separation/bundling of power and signal cables and wiring

Conduct and record any changes / modifications to system documentation under the appropriate controls and review in the IQ Summary Report.

Computer Operational Qualification (COQ) Preparation

COQ Protocols shall be developed to verify proper computer system operation with functional testing throughout all anticipated ranges and modes of operation. The operational tests shall be designed to challenge and demonstrate the computer control system's ability to operate in accordance with the approved System Specifications.

The design and structure of COQ testing shall be consistent with the control strategy of the process control system.

It is recognized that for Real-Time Process Control Systems a significant part of the COQ is to be conducted under process operational conditions, with suitable representative media being used in the process. This is particularly relevant to Loop Testing, Interlock Testing, and Recipe Testing.

COQ testing for the process control systems shall include the tests that follow:

Process Control System Operation and Procedures

A brief description of the computerized system's operation shall be provided in each COQ Protocol and shall include general operating modes and cycles. This section of the COQ is not intended to provide for any executable test activities, but rather to inform the reader of the system's operation.

A listing of all relevant SOPs shall be included and an approved set of SOPs made available for the COQ.

Input / Output (I/O) Testing

All I/O points shall be tested before any other computer control system operational testing is conducted in order to ensure that all the field devices are properly connected within the process control system, and are properly addressed and scaled within the code.

Each I/O point of the computer system shall be verified visually using the appropriate process control system programming software (installed on a dedicated PC) to ensure that each field device functions and is correctly addressed to the system. Each input shall be tested from the field device to the process control system up to and including the system memory location (register) where the process value (variable) is stored and/or used as part of the control loop algorithm. In addition, the proper addressing from the process control system memory location (register for the process value) to the workstation screens shall be verified. Each output shall be tested from the workstation screens to the system memory location to the field device. Upon completion of this testing, all further COQ testing can be performed for the process control system and/or process control system workstation with little or no need to verify the actual field device itself, since correct I/O addressing has been established.

Field devices, including analog and digital components, shall include (but are not limited to) the following examples:

Inputs	**Outputs**
Limit switches (valves)	Solenoid valves
Pressure sensors	Motors
Temperature sensors	Control valves
Level sensors	
Bar-code scanners	

In addition, panel mounted devices such as switches, indicator lights, and audible alarms shall be verified as part of I/O testing.

Operator Interface Testing

The operator interface testing will include, at a minimum, the following tests:

Displayed data
Boundary limits
Historical trend data
Reports/Data archiving
Screen graphics and navigation
Manual operation

The interfaces between the application and the system operatives shall be tested for proper operation. These shall include (but not be limited to):

Menu selections via keyboard
Menu selections via mouse
Keyboard Mapping if applicable (e.g., Shift F2 for Command Key 14)
Buttons such as Cancel, OK and Exit
Selection items such as checkboxes

This test may be combined with Functional Testing.

Displayed Data

Displayed data testing shall be conducted to verify that all data transferred from each of the process control system addresses (registers) is accurately transferred and displayed on the appropriate workstation screen. A verification that all displayed data fields such as the status of a pump or valve (e.g., on/off, open/closed, color) are displayed accurately shall be done. Scaling or proper conversion of analog inputs / outputs shall be verified to indicate that the workstation displays the proper value relative to the value in the appropriate system register. When data is displayed on more than one (1) screen, verification shall be performed on each screen displaying the data. In addition, data which is being transferred between process control system and other integrated databases shall be tested for accuracy and proper display on the workstation.

For workstations sharing the same process control system database (nodes) for display data, the following comparison must be conducted to ensure display data identity between all workstations in lieu of testing the accuracy of data displayed on each workstation.

Comparison of all screen files to the previously qualified workstation using a software compare utility.

Boundary Limits

Boundary limit testing shall be performed for each parameter which is changeable or can be modified as part of normal operation or modification of alarm limits and setpoints. This test will verify that entries at and within their specified boundary limits and of the specified data type are accepted by the process control system workstation and are transferred to the correct process control system register. Entries outside the boundary limits, or not of the correct data type, are not accepted by the process control system workstation and are not transferred to the process control system.

Historical Trend Data

The historical trend data test shall be performed to verify that specified historical trend data groups are defined for specified trend data points with respect to tag names, sample intervals and scaling (graph limits), and graph accuracy for each process control system workstation. In addition, the historical trend data functions will be tested by verifying that the data is being trended.

Reports / Data Archiving

Report testing shall be performed to verify that specified reports are defined and the data being reported from the process control system to the process control system workstation is accurate. Verification of reports will include (but not be limited to) the following:

- Alarm reports
- Batch reports
- Other client-defined reports

Data archiving tests shall be performed to verify that data is being archived at specified intervals and events to the correct files at each process control system workstation where data is being archived.

Screen Graphics and Navigation

Each process control system workstation process graphics (system overviews) screen shall be accessed to verify that the screen has all of its specified data fields and graphics. In addition, functional testing will be performed in order to verify that each screen can be accessed according to the specified menu tree (e.g., Process Data Screen - Historical Trend Data Display).

Functional Testing

All GMP-related functions described in the system specifications shall be tested. First, gain an understanding of all software functions and data flows. Functional tests are not to be written one at a time but should be part of an overall strategy to test the maximum possible number of test cases.

There may be several methods of testing each functional aspects of an information system. This combination of methods leads to a combinatorial explosion of possible paths to test the overall information system. Typically, it is not feasible to test all possible combinations or paths. The client system and process specifications must be utilized to decide the test cases to be included in the protocol. At a minimum, all possible paths required to meet process requirements must be tested. Usually, it is also possible to test additional test cases at the same time without much increase in effort.

With the above guidelines in mind, careful consideration should be given to design different test cases that would test as many system paths as possible. Once this is done, you can start writing the functional tests. Create the data items that are required to implement the test cases. Functional tests can now be written that build on one another to test the overall system.

Functional Branching Test

As applicable, all system menus, sub-menus and screens shall be tested for conformance to system documentation. Verify that all menus and sub-menus described in the manuals are accessible and that all screen layouts and fields are as described in the system documentation. This test can be performed in conjunction with Functional Testing. It is recognized, however, that it may not be feasible to perform this test for each specific screen for an information system with many screens.

Field Specifications Testing

As applicable, critical fields (i.e. fields affecting GMP-related functions) shall be tested for the following:

- Unique fields: Test that a new record can not be saved with a non-unique entry for a unique field.
- Required fields: Test that a record can not be saved with no entry for a required field in the record.
- Format: Verify that only valid entries are accepted (e.g., date entry in the specified format) and valid entries are not accepted (e.g., number of decimal points).
- Range: Test numeric field ranges by entering five (5) values for each field: below the lower limit, at the lower limit, above the upper limit, at the upper limit, and between the two limits.
- Validated field: A validated field is one where the field entry is validated against a pre-defined list of values. Verify that an entry which is not in the pre-defined list is not accepted and saved.

Concurrent Access Testing

As applicable, for a networked system, verify that concurrent access to a record or field does not compromise data integrity. Retrieve the same database record from two different sessions. Modify the record in both sessions and attempt to save it. Verify that the appropriate database locks and security mechanisms are in place to maintain data integrity.

Test remote control of system across network, identifying those access rights from remote sites (including suppliers).

Error Message Testing

Test all specified error messages. This test can be performed in conjunction with other OQ tests such as Field Specifications Test and Functional Testing since it may be easier to create error conditions in those sections.

Data Integrity Testing

Tests shall be devised to check the integrity of data within the Process Control System and all associated networks / interfaces within the GMP environment and interfaces with non-validated systems . In-built system diagnostics and interfaces to other systems will be checked during the course of this testing.

Local Mode

Operation Testing shall be performed to verify that the system can be operated in a local mode of operation from the process control system workstation. Testing will include (but will not be limited to) the following:

Manual operation of the valves, pumps, motors, etc.
Softkey functions
Initiation of process cycles

Security Testing

Physical Security

- Process Control System Node(s)/Network Server

The physical security of the process control system nodes and/or network server will be checked to verify that the room in which each is installed has restricted access.

- Process Control System Hardware/Software

The security of the process control system programming software and required hardware/software interface used to access the application programs shall be checked to ensure that the programming software and required hardware/software interface are stored and maintained with restricted access.

System Software Access

- Process Control System Access

The System Access test shall be performed to verify that access to each process control system workstation at each security level is granted only when a valid password has been entered by the appropriate system operator, and to verify that access is not granted when an invalid password has been entered. In addition, access to process control system workstation screens, functions, and operations, etc. where specific system operators have authority shall be verified using a valid password for each security level. It shall be verified that access to screens, functions, and operations, etc. that a system operator does not have authorization for is not granted. This testing will include (but will not be limited to) the following screens, functions, and operations:

- Analyze alarms
- Parameter modifications
- Automatic/manual control
- Create/change passwords
- Historical Trend Data
- Node shutdown
- Task switching

Alarm Testing - Eventful Operation

Alarm Testing shall be conducted to verify that all process control system alarms and warnings operate properly and in accordance with the System Specifications. Alarm testing shall be designed to verify that the system responds to alarm conditions and also to verify that the system responds once an alarm condition has been acknowledged and cleared.

In addition to specified alarm conditions, other eventful modes of operation which may or may not generate an alarm shall be tested (e.g., during sterilization cycle, the exposure time will reset if the chamber temperature falls more than 2°C below the temperature setpoint.)

Alarm Testing shall be conducted in a sequential path format with a focus on conditional/functional testing of software variables (e.g., I/O addresses, timers, counters, etc.) Alarm conditions will be simulated and the response of the system shall be verified using the appropriate process control system programming software in an on-line mode, as well as verification at the process control system workstation. The state or value of the specified software variables shall be verified. Particular attention shall be paid to the state of I/O addresses which define the general path for each specified alarm condition.

Alarms which are being displayed and reported on the process control system will be functionally tested at three (3) points: one significant figure above, below, and at the setpoint. This will ensure that the process control system workstation accurately displays and reports that the alarm is at its specified alarm limit and that it is reset according to its reset (deadband, hysterisis) value.

Verification of alarms will include (but will not be limited to) the following types of alarms:

- Alarm message on process control system workstation screen
- Alarm history file to process control system process database
- Process control system printer(s)
- Audible Enunciator
- Visual alarm indicators
- System response
- Alarm status between process control system and other integrated systems

Interlock Testing

Interlock Testing shall be conducted to verify that all interlocks with other equipment and systems (both mechanical and electronic) operate properly and in accordance with the System Specifications. Some examples of equipment and system interlocks include (but are not limited to) the following:

- Autoclave sterile/non-sterile doors (e.g., opening/closing)
- Integration between packaging line components (e.g., labeler/shrink wrapper, shrink rapper/cartoner)
- CIP/SIP connections to a system (e.g., proximity switches)
- Loading/unloading stations
- Integrated scales/balances
- Vessel jacket services
- Blending lines
- Multi-stream routing
- Status of other systems or equipment

Control Loop Testing

Control Loop Testing shall be conducted to verify the ability of the process control system to control critical parameters. Testing shall be designed to challenge the control of parameters throughout the specified range of operation of a minimum of three (3) representative setpoints (e.g., high, low, and midrange). Control loops specified to operate at one setpoint will be tested only at that setpoint.

Control Loop Testing shall require an upset to a stable, controlled parameter (process variable). The percentage of upset shall be pre-determined and in most cases will involve a change in setpoint. However, a manipulation in the actual controlled parameter shall be considered the preferred method of upset to a stable system whenever possible. In addition, most loops will require the normal load for adequate evaluation. Once an upset to a stable parameter has been initiated, the control loop shall be evaluated based on the following criteria:

- Maximum deviation from setpoint (overshoot)
- Percentage of overshoot from setpoint
- Response time required to reach stability at setpoint (recovery time)
- Maximum deviation from setpoint after system has stabilized

Control Loop Testing shall be conducted for critical controlled parameters which may include (but not be limited to) the following:

- Temperature
- Pressure/vacuum
- Relative humidity
- pH
- Flow
- Level

Recipe Loading Testing

Batch-specific information which resides at the process control system workstation process database shall be tested for proper data transfer and data integrity within the process control system. Testing will include verification of the recipe's operating parameters, alarm limits, and setpoints to be downloaded accurately from the process control system workstation. The selected recipe parameters shall be verified to ensure that each parameter has been downloaded accurately to the specified process control system Registers. Recipe Parameters shall include (but not be limited to) the following:

- Heat-up times/holding times/ Cool-down times
- Mixing speeds and times
- Pressure/Vacuums
- Conductivity/Resistivity
- Temperatures
- Alarm limits
- Operator instructions

Testing shall be conducted using the worst case recipe, e.g., a recipe with the largest number of parameters. Testing will also be performed to verify that data uploaded from the process control system is transferred correctly to the workstation database and that the new recipe parameters are downloaded properly as stated above.

If there is recipe data downloaded to multiple process control systems, the specified recipe information required for each process control system will also be verified.

Sequence of Operation Testing will be designed to functionally test programmed cycles, functions, and modes of operation based on normal system conditions. Some examples of programmed cycles and modes of operation include (but are not limited to) the following:

- Autoclave Cycles (e.g., Vacuum, Sterilization)
- Lyophilizer Cycles (e.g., Freeze Drying, Defrost, SIP, CIP)
- Sanitization Cycles (Water Systems)
- Recirculation/Drain Cycles (Water Systems)
- Blowdown Cycles (Distillation Equipment)
- Local/Remote Modes of Operation (All Systems)
- Mixing, Heating, Cooling Times (Compounding)
- Speed/Torque Curves (Compounding)
- Other System or Equipment-Specific Cycles and Modes of Operation

All programmed algorithms and calculations (e.g., F_o calculations, statistical analysis) performed by the process control system shall be verified as a part of Sequence of Operation Testing.

The methodology for Sequence of Operation Testing shall be virtually identical to Alarm Testing (6.3.4). Sequence of Operation Testing shall be conducted in a sequential path format with a focus on conditional/functional testing of software variables (e.g., I/O addresses, timers, counters). Cycle/mode initiation conditions and sequential cycle step conditions shall be simulated and the system response verified using the appropriate process control system programming software in an on-line mode and on the process control system workstation screen. The state or value of the specified software variables shall be verified. Particular attention shall be paid to the state of I/O addresses which define the general path for each specified cycle/mode condition.

Shut-down / Start-up Testing

Conduct controlled Shut-down and Start-up tests at key and random points in the process operation to verify that the computerized system can function safely and satisfactorily under such conditions, and enable record of any data loss.

Loss of Power Testing

Loss of power testing shall be conducted to ensure that when power is removed from the process control system, the equipment or system shall revert to a fail-safe state in which motors and pumps are shut down and valves revert to their failed positions. In addition, the retention of critical data in the form of setpoints, counters, timers, and process data will be verified. Testing shall also be designated to verify that when power is restored, the process control system returns to a predictable state and can be restarted. Varying duration of Power Loss shall be tested (e.g. milli-seconds, minutes etc). Loss of power testing shall also be conducted to ensure that when power is removed from the process control system workstation, the process control system and equipment will continue to operate, and that when power is restored to the workstation, communication will be established with the process control system. This testing will include (but will not be limited to) the following verifications:

- Process Control System workstation enters a defined shutdown procedure
- Process Control System and equipment enter a fail-safe condition
- Process Control System workstation data exchange with the Process Control System
- Process Control System workstation communication established with the Process Control System
- Communication failures and/or interrupts between
- Two Process Control System and workstation
- Process Control System and network server

Computer control systems which are supplied with an non-interruptible power supply (UPS) shall be tested to ensure that when power to the process control system workstation is removed, the UPS system will supply power to the system. Verifications will be made to include whether:

- System continues to operate
- Data exchange is maintained

Loss of Power Testing shall be conducted during each mode of operation, cycle, or phase of a cycle to ensure that the system performs as expected when power is removed and restored.

Environmental Testing

The environmental conditions to which the process control system and/or the process control system workstation are exposed to shall be monitored and recorded using a calibrated instrument over a period of time sufficient to ensure that the temperature and relative humidity conditions within the process control system and/or process control system workstation cabinets are within the manufacturer's specifications. Environmental Conditions Testing shall also include Process Control System Electro-magnetic Capability (EMC) testing (or certification), and Radio Frequency Interference (RFI) testing when process control systems are installed in an environment where the use of two-way radios is prevalent (e.g., technical and mechanical rooms.)

System Software Backup

Upon completion of COQ testing, a backup of the process control system Application Programs (source code) and the process control system workstation configured software, archived data, and network server shall be performed, and maintained as the official backup copy. This copy will replace the original backup copy created during the CIQ. The backup copies of the programs and files shall be scanned for viruses using the most current supplier or client-supplied virus detection utility. A printout of the executed scan shall be attached to the executed COQ, along with a complete listing of all programs and files in order to verify that all have been successfully scanned and no viruses were detected.

Contingency and Disaster Recovery Plan

Verify that a contingency and disaster recovery plan is in place to recover the information system in case of fire, earthquake, or other disaster.

Training Verification

Review all training records and documentation. Verify that all training documentation is current and that all operators have been trained in using the information system.

Operational Procedure Compliance Verification

Identify and review SOPs, observing their utilization by trained operators. Ratify any revisions to those SOPs.

Conduct and record any changes / modifications to system documentation under the appropriate controls and review in the OQ Summary Report.

Performance Qualification

For each multiple-node, network process control system, including a network server, a PQ Protocol shall be developed to verify that the complete computerized system, with all its components, will accurately and consistently perform under production conditions. Typical process operation activities which shall be performed may include (but are not limited to) the following:

- Weighing of ingredients
- Formulation of ingredients
- CIP/SIP of process tanks
- QA/QC sampling
- Filling process
- Warehouse management

The degree of testing will influenced by the amount of OQ testing already conducted and shall include (but not be limited to) the following:

- Confirm applicability of operating procedures
- Check production records against plant log books.
- Monitor GMP critical parameters.
- Monitor alarms and messages.
- Confirm security access procedures.
- Confirm operator interface is fully functional.
- Start-up and Close-out batch.
- Confirm collection and check reproduction of batch records.
- Confirm batch records are correct.
- Check viability of contingency plan.
- Check backup and restoration procedure.

Automated batch records must provide accurate reproduction of master data and equivalent assurance to a double manual check, noting that manual checks can identify and record unexpected observations. Computerized

systems releasing batches need authorization for each batch, and the responsible person should be recorded against the batches. All batch records require quality control inspection and approval prior to release and distribution of the product. The identity of operators entering or confirming data should be recorded. Authority to change data and reasons for the change must be recorded in an audit trail.

Computerized system PQ testing for manufacturing batch operations (under client-defined maximum production conditions) will be designed to evaluate the network's performance. Computerized system PQ testing will focus on all data integrity issues, including recipe uploading and downloading, and monitor computer system operating conditions such as CPU utilization, peak network traffic etc., verifying that they are within specified ranges.

Pre-operation activities which shall include preparing and approving of recipes which will be used throughout the production process.

Test scripts for each system operator should be created from the pre-defined manufacturing data. System operators will concurrently execute the test scripts. At a minimum, the number of operators for the test shall be equal to the maximum expected number of concurrent system operators.

Test result outputs must be compared with expected test results and verification that they are identical must be recorded.

All activities during PQ execution shall be monitored and any discrepancies or areas of improvement recorded.

Conduct and record any changes / modifications to system documentation under the appropriate controls and review in the PQ Summary Report.

APPENDIX NO. 10 SIEMENS QUALITY SYSTEM

Siemens Intranet contains details of Siemens Quality System
For information on how to access the Intranet, please contact the appropriate Quality Assurance Representative

APPENDIX NO. 11 SIEMENS AUDIT REPORTS :

APPENDIX NO. 11A SIEMENS COMPONENT DEVELOPMENT & PROJECT METHODOLOGIES

Summary

Based on our review[2] of documented policies, procedures, and records pertaining to the development, testing and support of the Simatic PCS 7 System, it is the opinion of Kemper-Masterson, Inc. (KMI) that, though opportunities for improvement exist, Siemens has developed and tested the Simatic PCS 7 System in a manner both consistent with good prevailing industry practice and adequate to insure a high-quality product.

It is also the opinion of KMI that the documentation of the development and testing procedures, and the system documentation which Siemens provides to the user of a Simatic PCS 7 application, are adequate to support the user's efforts to qualify and maintain the system application in a validated state meeting the GMP requirements of the United States Food and Drug Administration (US FDA).

To reach this opinion, KMI has reviewed the following areas:

- System compliance with applicable US FDA GMPs
- System specifications and capabilities
- Software development standards, procedures, and practices
- Software development documentation
- Software testing standards, procedures, and practices
- Software testing documentation
- Customer service policies, procedures, and practices
- Software version control and support policies, procedures, and practices
- System application development (project engineering) policies, procedures, and practices
- System configuration documentation and factory acceptance testing
- On-site commissioning policies, procedures, and practices.
- General quality systems and procedures

In each of the areas reviewed, Siemens provided documented evidence that its policies, procedures, and actual practices meet or exceed health care industry standards and requirements.

This, together with the exercise detailed in Appendix No. 11B, illustrates Siemens understanding of the in-depth examination that is necessary to support clients who are operating in a regulated environment.

[2] Kemper-Masterson Inc. in February 1997

APPENDIX NO. 11 SIEMENS AUDIT REPORTS :

APPENDIX NO. 11B SIEMENS COMPONENT GMP IMPACT ASSESSMENT

Summary

In February 1997 Kemper-Masterson Inc. were commissioned by Siemens to assess how the functionality offered by the SIMATIC PCS 7 Process Control System for applications in the Pharmaceutical Industry aligned with the Good Manufacturing Practice requirements of the US Food and Drug Administration.

KMI reviewed the following areas:

- System compliance with US FDA GMPs
- System specifications and capabilities

The exercise identified some attractive concepts and in-built functionality for pharmaceutical applications, and detailed functions that would have to be carried out and recorded in conjunction with written procedures.

Recommendations from the assessment are being undertaken by Siemens as part of the SIMATIC PCS 7 component development program.

With the increased utilization of automated systems at all levels in pharmaceutical drug development and production, Siemens recognizes the need to review the ever evolving GMP requirements and determine the impact on implementation and operation of their process control systems.

APPENDIX NO. 12 TERMS & DEFINITION, ACRONYMS AND ABBREVIATIONS

TERMS & DEFINITION

exist in SIMATIC electronic Manual, Order # 6ES7 398-8AE00-8AE0

ACRONYMS AND ABBREVIATIONS

APV	Arbeitsgemeinschaft für pharmazeutische Verfahrenstechnik e.V. International Association for Pharmaceutical Technology
AR	Annual Report
ATS	Acceptance Test Specification
AUT	SIEMENS Business Unit AUTOMATION through Sept. 1997; new acronyms will be introduced based on reconstruction of groups.
BACPAC	Bulk Actives Post Approval Changes
CBE	Changes being effected
CD	Compact Disk
CFCs	Continuous Function Chart
CFRs	Code of Federal Regulations
cGMP	to Current Good Manufacturing Practice
CIP/SIP	Clean-in-place/Sterilize-in-place
CIQ	Computer Installation Qualification
Cont. sys.	Control System
COQ	Computer Operational Qualification
COTS	Commercial-Off-The-Shelf
CPU	Central Processing Unit
DIA	Drug Information Association
DQ	Design Quality
EC	European Community
ECMA	European Computer Manufacturer Association
EFPIA	European Federation of Pharmaceutical Industries Associations
EMC	Electro-magnetic Capability
EMEA	European Medicines Evaluation Agency
ex.	Extend
FAT	Factory Acceptance Testing
FDA	Food and Drug Administration
FDA - CBER	FDA-Center of Biologics Evaluation and Research
FDA - CDER	FDA-Center of Drug Evaluation and Research
FDS	Functional Design Specification
FMEA	Failure Mode, Effects and Critical Analysis
FMECA	Identical with FMEA

FTA	Fault Tree Analysis
GAMP	Good Automated Manufacturing Practice , Supplier Guide
GMP	Good Manufacturing Practice
HAQCCP/HAZOP	Hazard Analysis and Critical Control Point / Hazard and Operability Study
HDS	Hardware Design Specification
HTS	Hardware Test Specification
HW	Hardware
I/O	input/output
ICH	International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use
IFPMA	international federation of pharmaceutical manufacturers Association
IKS	Interkantonale Kontrollstelle für Heilmittel
Intg.	Integration
IQ	Installation Qualification
ISO	International Standardization Organization
ISPE	International Society for Pharmaceutical Engineering
JPMA	Japan Pharmaceutical Manufacturers Association
LAN	Local Area Network
LIMS	Laboratory Information Management Systems
MCA	UK Medicines Control Agency
MES	Manufacturing Execution System
MHW	Ministry of Health and Welfare, Japan Regulations: MHW Ordinance No. 3, „Regulations for Manufacturing Control and Quality Control of Drugs„
MRP	Materials Requirements Planning
MRP II	Manufacturing Requirements Planning
N/A	NOT APPLICABLE
OQ	Operational Qualification
P&IDs	Pipe and Instrumentation Diagrams
PA	Prior approval
PAC-SP	Post Approval Changes for Sterile Parenterals
PCs	Personal Computer
PCS	Process Control Systems
PDA	Parenteral Drug Association
PhRMA	Pharmaceutical Research and Manufacturing Association
PIC	Pharmaceutical Inspection Convention
PIC/S	Pharmaceutical Inspection Cooperation Scheme
PICSVF	Pharmaceutical Industry Computer Systems Validation Forum
PLCs	Programmable Logic Controllers
PQ	Performance Qualification
QA/QC	Quality Assurance / Quality Control
RAPS	Regulatory affairs professionals society
Reqt.	Requirement

RFI	Radio Frequency Interference
RFQ	Request for Quotation
SAT	Site Acceptance Tests
SC Supplier	standard components supplier
SCADA	Supervisory Control and Data Acquisition Systems
SDS	Software Design Specification
SFCs	Sequential Function Chart
SI	System Integrator
SMDS	Software Module Design Specification
SMITS	Software Module Integration Test Specification
SMTS	Software Module Test Specification
SOP	Standard operating procedure
SOPs	Standard operating procedures
Spec.	Specification
SQA	Software Quality Assurance
SQAP	Software Quality Assurance Plan
SQL	Structured Query Language
SUPAC	Scale Up and Post Approval Changes
SUPAC-IR	SUPAC-Immediate Release
SUPAC-MR	SUPAC-Modified Release
SUPAC-SS	SUPAC-Semi Solids
SUPAC-TDS	SUPAC-Transdermal Delivery Systems
SW	Software
TGA	Therapeutic Goods Administration; Commonwealth Department of Human Services and Health; Regulation Australian Code of Good Manufacturing Practice for Therapeutic Goods - Medicinal Products
URS	User Requirement Specification
USA	United States of America
VFA	Verband forschender Arzneimittelhersteller
WHO	World Health Organization

APPENDIX NO. 13 REFERENCE LITERATURE :

APPENDIX NO. 13A PDA TECHNICAL REPORT NO. 18, VALIDATION OF COMPUTER-RELATED SYSTEMS

APPENDIX NO. 14 GENERAL GMP / VALIDATION NOTES

The following notes have been compiled, based on recognized GMP / Validation publications and seminars and are intended for general guidance and support for computerized system design and application in the pharmaceutical environment:

The FDA consider software to be documentation.

Pharmaceutical manufacturers may consider field instrumentation and devices to be an integral part of the computer system (also see NAMUR N.58, Execution of Process Control Projects subject to Validation, Section 1.2, Figure 1).

Raw Data may include photographs, microfilm copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments. Thus, consideration must be given to:

- Word Processing Files
- Electronic Signals Stored Magnetically
- Computer Database Files
- Electronic Signatures
- Electronic Audit Trail
- Graphic Images (Trend v. Data)

Regulatory Authorities have three major concerns regarding computer validation**:**

- Does the system perform accurately and reliably?
- Is the system secure from unauthorized or inadvertent changes?
- Does the system provide adequate documentation to support the process validation?
  - with focus on the following data issues:
    - controls
    - repeatability
    - security
    - integrity
    - traceability
  - and how this is achieved through structured and documented methods, and reports.

Where a computer is used in connection with any procedure or process associated with the production of therapeutic goods, the computer system employed should meet the requirements for those manual functions it is intended to replace. This entails providing appropriate SOPs for the system operator.

A logic flow diagram of a schematic for software should be prepared for critical evaluation against system design/ requirements/criteria.

A control document should be prepared specifying the objectives of a proposed computer system, the data to be entered and stored, the flow of data, the information to be produced, the limits of any variables and the operating program(s) and test programs, together with examples of each document produced by the program, instructions for testing, operating and maintaining the system and the names of the persons responsible for its development and operation

Records of defects, deviations found and resolved should be added to the history file.

Any change to an existing computer system should be made in accordance with a defined change control procedure which should document the details of each change made, its purpose and its date of effect and should provide for a check to confirm that the change has been applied correctly .

Data collected from manufacturing or monitoring equipment should be checked by verifying circuits of software to confirm that it has been accurately transferred.

The entry of critical data into a computer should require independent authority to verify and release for use.

Access to enter, amend, read or print out data should be defined and methods for the prevention of unauthorized entry should be available ie passwords or user identity codes

The computer system should create a complete record of all entries and amendments to the database

In the event of a breakdown a written procedure should be followed which will return the system to the actual process state. To ensure all programs and data necessary to restore the system are available a periodic check should be carried out .

Relevant data / information stored within the computer should be able to be printed out.

Printed sheets produced by the computer should be legible and in the case of printing onto forms should be properly registered

When validating a computer system in a FDA regulated application the following records should be available:

- General description of the system, the components and the operating characteristics
- Diagrams of hardware layout/interaction
- List of programs with a brief description of each
- System logic diagrams or other schematic form for software packages
- Current configuration for hardware and software
- Records of evaluation data to demonstrate system does as intended (verification stage and ongoing monitoring)
- Review of historical logs of hardware and software for development, start-up and normal run periods.
- Records of qualified operator access

- Details of access security levels/controls
- Procedure for ongoing evaluation
- Range of limits for operation variables
- Change controls required for system and program alterations (validation, responsible persons, approval, implementation & records)
- Storage of hard copies of electronic data for auditing purposes
- Secure storage of data to prevent damage
- Data back-up and separate storage

Siemens AG
A&D AS E 146

Östliche Rheinbrückenstr. 50
D-76181 Karlsruhe
Federal Republic of Germany

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- ❐ Electrical Machinery
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- ❐ Pulp and Paper
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