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Computer System Validation: Controlling the Manufacturing Process

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I. INTRODUCTION

Pharmaceutical product research, development, manufacturing, and distribution require considerable investment in both time and money, and computerization has become key to improving operational efficiency. Computer system application is expected to support the fundamental requirement of minimizing risk to product identity, purity, strength, and efficacy by providing consistent and secure operation and reducing the potential of human error. From the regulatory and business viewpoint, the advantages of utilizing computer systems can only be realized by ensuring that each system does what it purports to do in a reliable and repeatable manner.

The objective of this chapter is to examine computer system qualification as required for validation programs in the regulated pharmaceutical industry, providing guidance and reference on regulatory requirements, validation methodologies, and documentation.

The good manufacturing practice (GMP) regulations in focus are from the U.S. Code of Federal Regulations (CFRs) [1,13], as inspected and enforced by the Food and Drug Administration (FDA), and Annex 11 of the European Community (EC) *Guide to Good Manufacturing Practice for Medicinal Products* [2].

The validation methodology presented is consistent with that presented in the *Supplier Guide for Validation of Automated Systems in Pharmaceutical*

Manufacture, GAMP Forum/ISPE [3], the Parenteral Drug Association (PDA) technical report *Validation of Computer-Related Systems* [4], and the ISPE *Baseline Guide for Commissioning and Qualification* [5]. A number of issues that are fundamental to application engineering a computer system for controlling a manufacturing process are also addressed, and the required relationship to the validation life cycle is examined.

To consider the close links with the manufacturing process this chapter will focus throughout on computer systems and the associated field input/output instrumentation required for the direct control and monitoring of the manufacturing process. Here the traditional demarcation between "real-time" and "information" systems is fast disappearing with process control and automation systems now capable of providing significant levels of data processing and management for pharmaceutical manufacturing.

A. Validation Policy Considerations

Over the years regulatory authorities have identified three major concerns regarding computer system application.

Does the system perform accurately and reliably?
Is the system secure from unauthorized or inadvertent changes?
Does the system provide adequate documentation of the application?

With this in mind and to achieve and maintain validated computer systems, pharmaceutical manufacturers need to include the following as part of their compliance policy:

The master validation plan for each site must identify all computer systems operating in a GMP environment.
Computer system validation activities must ensure that all computer systems operating on the GMP environment perform consistently to the required standards.
All validation document preparation and activities must be performed in accordance with predefined and approved procedures.
The integrity of quality-related critical parameters and data must be maintained throughout each phase of the validation life cycle, including the supplier design and development phases.
Sites must operate a validation maintenance regime incorporating change control and revalidation programs.

II. REGULATORY BACKGROUND

A. Good Manufacturing Practice

The World Health Organization GMP [6] concept requires that critical processes should be validated, with validation defined as the documented act of proving

that any procedure, process, equipment, material, activity, or system actually leads to the expected results. The pharmaceutical manufacturer is expected to adopt current good practices to support evolving process and technology developments.

B. Regulations

Examples of the U.S. regulations applicable to computer system application in a GMP environment are shown in Table 1. The FDA also publishes compliance policy guides [7] related to pharmaceutical drug products and views the guidance provided on related products (e.g., medical devices [8]) to be "current" good manufacturing practice that should be considered for comparative GMP applications.

For the EC *Guide to Good Manufacturing Practice for Medicinal Products*, Annex 11 [2] identifies the following requirements that need to be addressed for computerized system application:

GMP risk assessment
Qualified/trained resource
System life-cycle validation
System environment
Current specifications
Software quality assurance
Formal testing/acceptance
Data entry authorization
Data plausibility checks
Communication diagnostics
Access security
Batch release authority
Formal procedures/contracts
Change control
Electronic data hardcopy
Secure data storage
Contingency/recovery plans
Maintenance plans/records

C. Validation

Good manufacturing practice regulations identify what controls must be in place and adhered to in order to be in compliance, but do not provide instruction on how to implement these controls. The methods used to ensure the product meets its defined requirements are the responsibility of the pharmaceutical manufacturer, who must be prepared to demonstrate GMP compliance with validated systems and formal records.

Table 1 Examples of U.S. Regulations Applicable to Computer Systems

CFR	Title	System Impact
People		
21 CFR 211. 25	Personnel qualifications	Qualifications, training, and experience for assigned functions
21 CFR 211. 34	Consultants	Qualifications, training, and experience to provide the service Record qualifications and work undertaken.
Hardware		
21 CFR 211. 63	Equipment design, size, and location	System design, capacity, and operating environment
21 CFR 211. 67	Equipment cleaning and maintenance	Preventative maintenance program at appropriate intervals, to formal procedures identifying responsibilities, schedule, tasks
21 CFR 211. 68 (a)	Automatic, mechanical, and electronic equipment	System reliability, with routine calibration, inspection or checks to formal maintenance procedures; results to be documented.

Software		
21 CFR 211. 68 (a), (b)	Automatic, mechanical, and electronic equipment	Accuracy, repeatability, and diagnostics Application software documentation Configuration management Access security Input/output signal accuracy and device calibration Data storage Software backup, archiving, and retrieval
21 CFR 211. 100	Written procedures: deviations	Formal approved and documented procedures (software) Deviation reporting
21 CFR 211. 101 (d)	Charge-in of components	Automated component addition verification
21 CFR 211. 180 (a), (c), (d), (e)	General requirements (records and reports)	Data record availability, retention, storage medium, and reviews
21 CFR 211. 182	Equipment cleaning and use log	Maintenance records
21 CFR 211. 186 (a), (b)	Master production and control records	Application software documentation
21 CFR 211. 188 (a), (b)	Batch production and control records	Data reproduction accuracy Documented verification of process steps Operator identification
21 CFR 211. 192	Production record review	Data record review by quality control
21 CFR 11	Electronic records; electronic signatures	Electronic record/signature type, use, control, and audit trail
FD&C Act, Section 704 (a)	Inspection	Access to computer programs

Source: Refs. 1, 13.

Validation is a process that involves planned activities throughout the life cycle of the computerized operation.

The recognized methods of conducting validation are outlined below.

Prospective validation, which includes all main validation phase approvals by means of design qualification (DQ), including specification reviews, installation qualification (IQ), operational qualification (OQ), performance qualification (PQ), and ongoing evaluation.

Retrospective validation, which may be conducted when sufficient historical records are available to demonstrate controlled and consistent operation (e.g., historical process data, problem logs, change control records, and test and calibration documentation).

Concurrent validation, in which documented evidence is generated during the actual operation of the process, is sometimes adopted in clinical supply situations in which only limited material is available for the trials.

Whatever the validation approach, the fundamental requirement for computer system validation is to establish documented evidence that provides a high degree of assurance that the system consistently operates in accordance with predetermined specifications. The EC guide to GMP also requires periodic critical revalidation to be considered to ensure processes and procedures remain capable of achieving the intended results.

For new applications or projects a prospective validation based on a recognized life cycle is the most effective and efficient approach. The life-cycle methodology can also be adapted for existing systems that do not have adequate documented records to support a retrospective validation.

Industry groups and regulatory authorities have debated and addressed the issues surrounding computer system validation, with the PDA [4] and GAMP Forum [3] providing industry guidance on validation life-cycle methodology and documentation.

Furthermore, the ISPE *Baseline Guide*, *Commissioning and Qualification* [5] emphasises the need to undertake qualification practices only for equipment and system component parts and functions that could directly impact quality attributes of a product or process. Other components and functions are to be dealt with under good engineering practice (GEP) [3,5] throughout the system life cycle, undergoing an appropriate level of documented commissioning.

D. Computerized Operation

The computer systems that can directly impact the quality attributes of pharmaceutical drug products and associated production records include a wide range of applications. Typically candidate systems can include real-time process control/

manufacturing automation systems (as examined herein), analytical systems, laboratory information systems, environmental management systems, process management information systems, material management, warehousing and distribution systems, document management systems, and maintenance systems.

Within the scope of validation for an automated facility or plant, the computer system is a component part of the facility GMP operation. The components of this computerized operation are illustrated in Figure 1, which depicts the composition of the computer system and the operation that it controls and monitors. In the case of real-time applications for primary (bulk) production process control systems and automated secondary manufacturing systems this will normally encompass the associated field instrumentation and electrical and pneumatic regulating devices (actuated valves, motor controls) and interconnecting cabling/wiring/piping. Together with the production/manufacturing equipment, the process and approved standard operating procedures (SOPs) are elements of a computerized operation.

The operating environment within which the computerized operation must function represents the defined work flow and support procedures between peo-

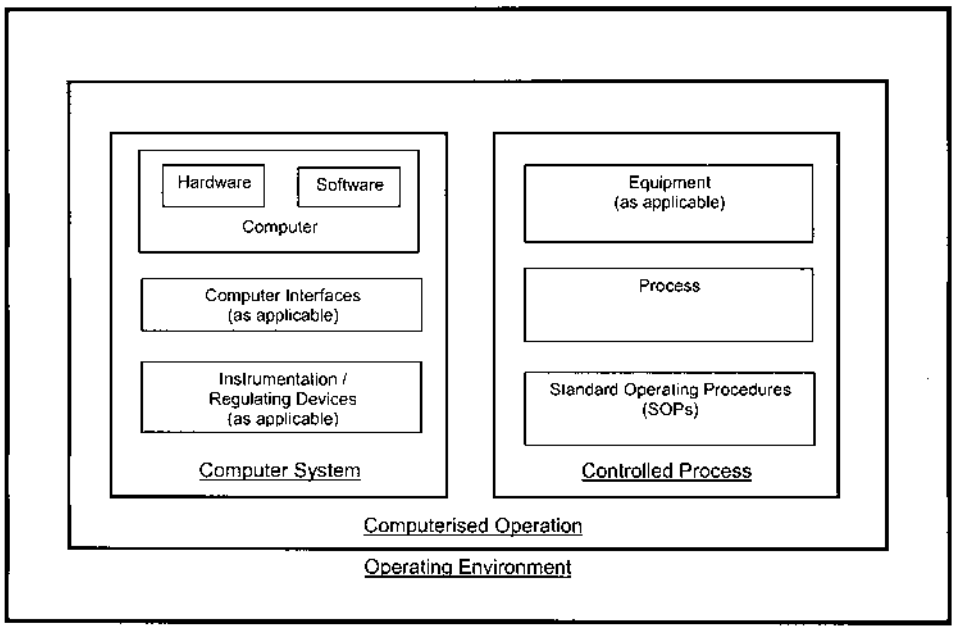


Figure 1 Computerized operation model.

ple and the computerized operation and typically encompasses the following controls and procedures:

System incident log
System maintenance program
Instrument calibration schedule
Environmental conditions
Support utilities and services
Security management
Change control
Configuration management
Inventory control
Document control
Internal audit
Training program
Contingency/recovery plans
Validation documentation file

To maintain control of the computer system throughout its conception, implementation, and operational use in a GMP environment, it is required that the computer system application must be validated in a way that will establish auditable documented evidence that the computer system does what it is expected to do. As applicable, this needs to be carried out in conjunction with plant equipment to provide a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes. The methodology to achieve this is based on a recognized life-cycle mode.

III. VALIDATION LIFE CYCLE

Providing documented evidence to achieve and maintain the validated status and uphold GMP compliance requires a systematic approach and rigorous controls throughout all phases of the computer system validation life cycle. Formal testing at key stages in the life cycle will provide records to demonstrate that predefined requirements have been met and that the computer system is fully documented.

A. Validation Process

The validation of a computer system involves four fundamental tasks.

Defining and adhering to a validation plan to control the application and system operation, including GMP risk and validation rationale
Documenting the validation life-cycle steps to provide evidence of system accuracy, reliability, repeatability, and data integrity

Conducting and reporting the qualification testing required to achieve validation status

Undertaking periodic reviews throughout the operational life of the system to demonstrate that validation status is maintained

Other key considerations include the following:

Traceability and accountability of information to be maintained throughout validation life-cycle documents (particularly important in relating qualification tests to defined requirements). The mechanism (e.g., matrix) for establishing and maintaining requirements traceability should document where a user-specified requirement is met by more than one system function or covered by multiple tests

All qualification activities must be performed in accordance with predefined protocols/test procedures that must generate sufficient approved documentation to meet the stated acceptance criteria.

Provision of an incident log to record any test deviations during qualification and any system discrepancies, errors, or failures during operational use, and to manage the resolution of such issues

B. Support Procedures

To control activities associated with the validation program the following "cornerstone" procedures need to be in place and in use:

GMP compliance and validation training—to an appropriate level commensurate with the individual's job function

Inventory management—to ensure all computer systems are assessed and designated as GMP or non-GMP systems

Document management and control—to ensure the availability of current approved documentation and an audit trail of all records related to the validation program

Configuration management—to ensure system software and hardware configuration and versions are controlled by authorized personnel

Change control—to ensure any change to the system—or to other equipment that may affect system use—is properly assessed, documented, and progressed with regard to GMP compliance and system validation

It is also recognized that satisfactory implementation, operation, and maintenance of a computer system in the manufacturing operating environment is dependent on the following:

Quality management system—to control and document all aspects of the pharmaceutical GMP environment, including provision of a comprehensive set of SOPs to provide written and approved procedures that enable activities to be conducted and reported in a consistent manner

Good engineering practice—to establish engineering methods and standards that must be applied throughout the system life cycle to deliver appropriate, cost-effective solutions that underpin the validation program

C. Validation Life Cycle

The established methodology for computer system validation enables identification and control of each life-cycle phase and its associated document deliverables. It is also recognized that throughout the validation life cycle there is a level of dependency on the methods, services, and resources of the computer system supplier.

The V model in Figure 2 illustrates the key life-cycle activities for prospective validation, ranging from validation planning to system retirement. It is a recognized methodology for computer system applications and illustrates the links between system planning, requirements and design specifications, and the corresponding reviews and qualifications. It includes the supplier design, development and testing of software modules, and the integration and testing of the combined software and hardware [10]. When successfully executed, each task on the life cycle will result in documented evidence, including a formal report, to support the validation program and ensure a controlled step to the next phase. Formal qualifications must be conducted for system design, installation, operation, and performance. The relationship to the manufacturing process is introduced through the link with PQ to the process validation report. Ongoing evaluation of the system provides confirmation of the validation status of the system throughout its operational life in the GMP environment. Formal decommissioning will ensure accurate data are archived to support released product.

The validation life-cycle phases align closely with the project stages for new computer system applications. With this in mind, it is recognized that a significant proportion of the documentation required for validation may be generated by a well-controlled and -documented project.

The process for implementation and prospective validation of computer systems outlined in Figure 3 depicts the system application activities within each life-cycle phase and identifies key issues and considerations for each step. The process includes for evaluation of both the computer system product and the system supplier's working methods. The same life-cycle approach may be applied to validate the associated control and monitoring instrumentation [9].

D. Existing System Validation

For retrospective validation, emphasis is put on the assembly of appropriate historical records for system definition, controls, and testing. Existing systems that are not well documented and do not demonstrate change control and/or do

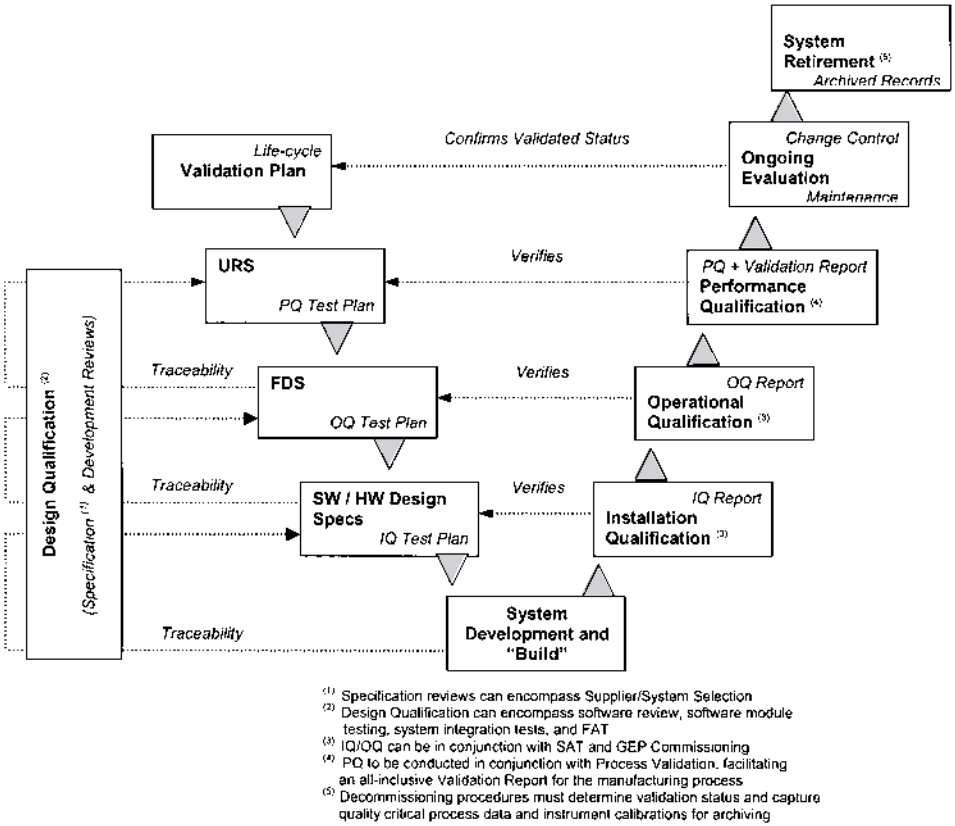
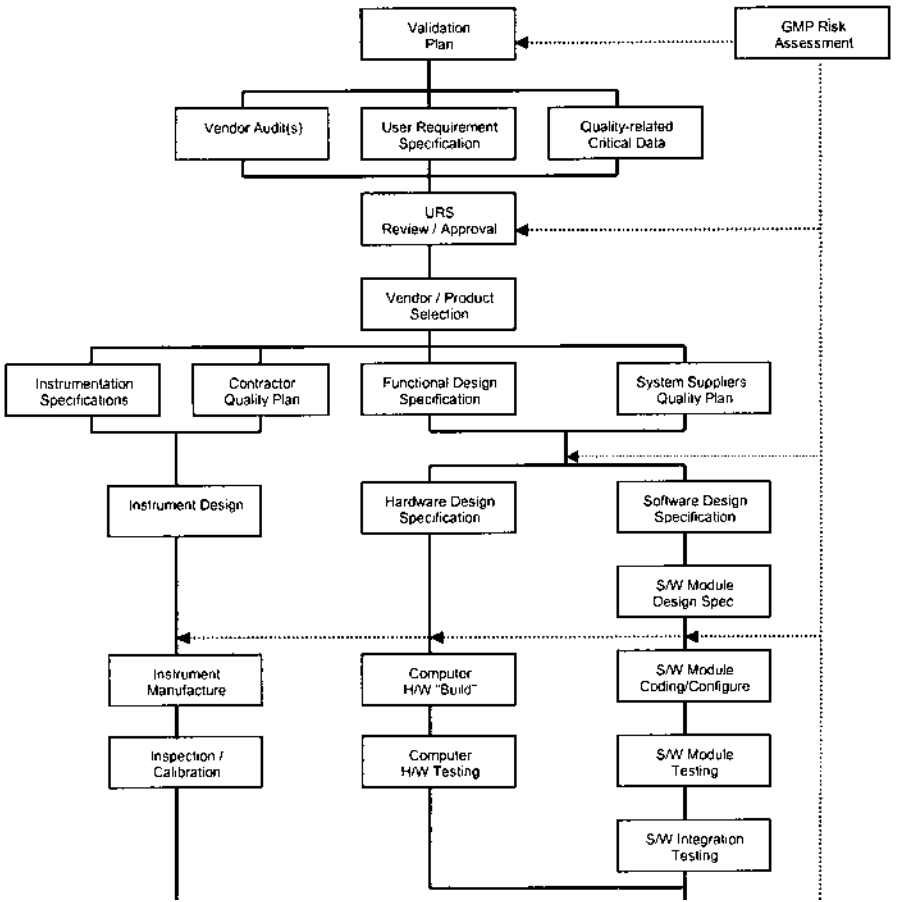


Figure 2 Framework for system validation.

not have approved test records cannot be considered as candidates for retrospective validation as defined by the regulatory authorities.

Consequently, for a system that is in operational use and does not meet the criteria for retrospective validation, the approach should be to establish documented evidence that the system does what it purports to do. To do this, an initial assessment is required to determine the extent of documented records that exist. Existing documents should be collected, formally reviewed, and kept in a system "history file" for reference and to establish the baseline for the validation exercise. From the document gap analysis the level of redocumenting and retesting that is necessary can be identified and planned.



LIFE CYCLE ISSUES

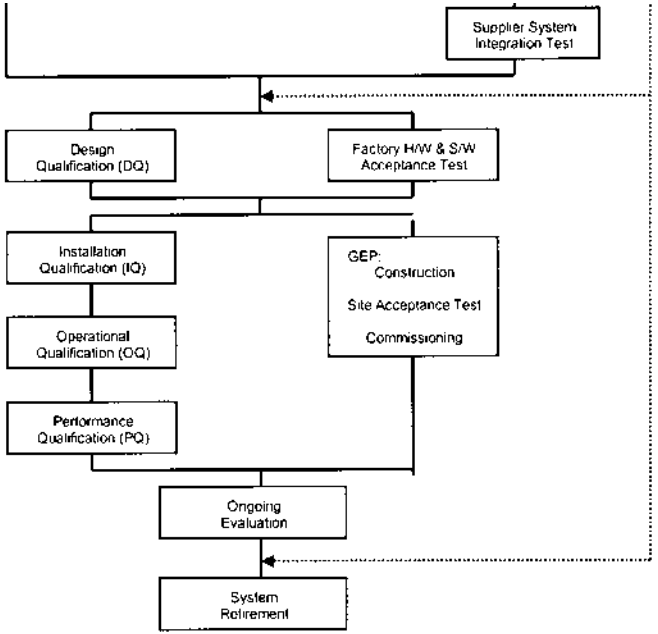
Planning
- Key planning documents, control procedures and training in -place
- System boundaries defined
- Decision to validate and rationale

Definition
- PQ Protocol test criteria derived from and traceable to Requirement Specification
- The Requirement Specification should be formally reviewed and approved. In particular, the requirements for quality-related critical parameters, data and system functions should be verified.

Supplier Selection
- Supplier selection criteria and audit should cover working methods, system functionality, and GMP knowledge

Design / Development & "Build"
- OQ Protocol test criteria derived from and traceable to Functional Specification
- IQ Protocol verification/test criteria derived from and traceable to Design Specifications
- Conduct Software Review" to check the code or configuration is to specification, programming standards and provides maintainable software
- System design and development testing under Supplier's Software Quality Assurance Program
- Review against Quality & Project Plan

Design Qualification (Review)
- DQ ensures system development activities are undertaken in a controlled manner, with reviews of system specifications, development procedures and testing documentation in support of the validation programme



- For more complex systems the design qualification can be accomplished by reviewing key activities throughout system development
- Pre-delivery (FAT) and post-delivery (SAT) acceptance tests to align with the Qualification test procedures as far as possible.

Qualification & Commissioning
- Qualification testing for system elements and functions that *directly impact* product / process quality and associated data
- Good Engineering Practice (GEP) and documentation for commissioning of system elements and functions that do not directly impact product / process quality
- Tests to be traceable to requirements
- IQ/OQ can be in conjunction with SAT
- OQ/PQ testing to include SOP's
- Each Qualification phase to be formally reported
- A Validation Report and Validation File are the main deliverable

On-going Evaluation
- Periodic Review(s)
- Internal Audit Report(s)
- Critical Data Records
- Software Records
- Life-cycle Documents Update
- Maintenance Procedures
- Calibration Records
- Configuration Control Records
- Change Control Records
- Risk Assessment Records
- Disaster Recovery and Contingency Plan
- Re-validation
- De-commissioning Plan
- Document Control

Figure 3 Computer system development and validation process.

Existing system applications will need to be evaluated and applicable GMP issues and risks identified. Whether it be legacy systems, systems to be revalidated, or systems yet to be validated, the critical parameters, data, and functions that directly impact GMP should be clearly identified and formally documented. Each system should be assessed under a formal procedure to determine compliance with the regulations for electronic records and electronic signatures. Any resulting action plan should include system prioritization and implementation timings.

The methodology for validating existing computer systems will need to adopt life-cycle activities in order to facilitate the process of generating acceptable documented evidence (see Fig. 4). When coupled with an appropriate level of extended system performance monitoring and analysis during system operational use and maintenance, this can provide an effective method for validating existing systems.

For new or existing computer system applications, adherence to a life-cycle approach for validation will provide:

A framework for addressing the validation plan
Points at which the validation program can be controlled and challenged
Auditable documented records of system application and operational use

IV. PLANNING

The pharmaceutical manufacturer must establish effective policies and plans for regulatory compliance and validation to enable individuals to clearly understand the company commitment and requirements. Computer validation planning should ensure an appropriate training program, preparation of validation guidelines and procedures, system GMP compliance risk and criticality assessment, a documented validation strategy and rationale, clearly defined quality-related critical parameters and data for the manufacturing process.

A. Training

The pharmaceutical manufacturer must ensure that personnel are trained to an appropriate level in GMP and validation planning and requirements to enable them to adequately perform their function. This applies to any resource used in connection with GMP compliance and validation life-cycle activities and documentation. A training program should be in place and individual training records maintained. The records and suitability of external resources used by suppliers or contractors should also be examined.

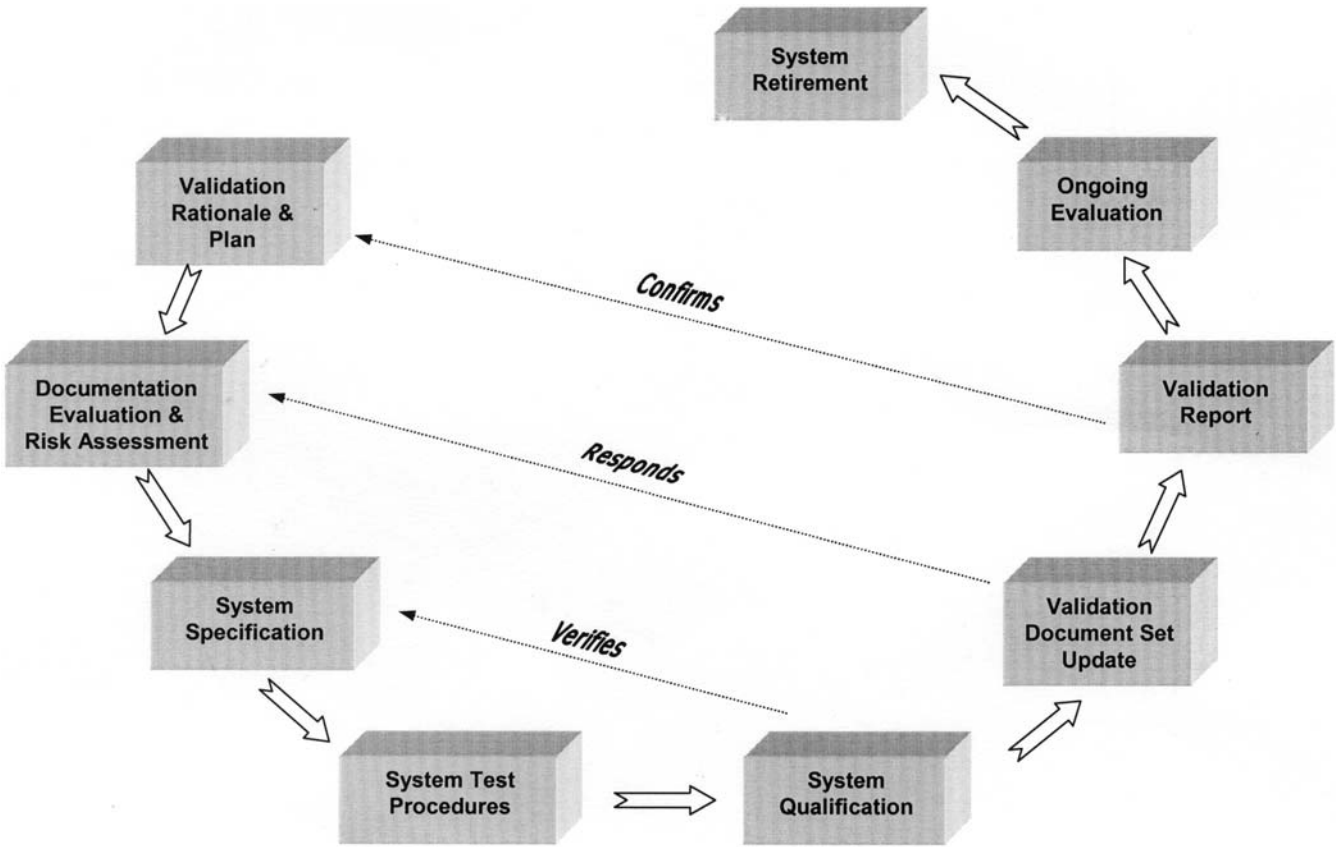


Figure 4 A validation cycle for existing systems.

B. Validation Organization

An organizational structure should be established to facilitate the qualification of computer systems operating in the GMP environment. The organization should be representative of the departments involved, and would typically include quality management, owner/user department, information technology, and engineering.

C. Validation Guidelines and Procedures

The regulatory authorities require the pharmaceutical manufacturer to maintain guidelines and procedures for all activities that could impact the quality, safety, identity, and purity of a pharmaceutical product. This includes procedures for implementing and supporting the validation life cycle and for process operation.

The pharmaceutical manufacturer will need to prepare written procedures that clearly establish which activities 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 review and approvals are required for each document. Each procedure must give detailed instruction for executing specific tasks or assignments, and should be written in accordance with the pharmaceutical manufacturer's procedure for writing and approving standard procedures and guidelines. For each document the meaning and significance of each signatory must be defined.

Standard operating procedures will be required as written instruction to operating personnel on how to operate the manufacturing process. These will cover operation in conjunction with the computer system and also any tasks that are independent of the computer system. Where there is a requirement for quality-critical data to be manually entered on the computer system, there should be an additional check on the accuracy of the entry. If the computer system is not designed to carry out and record this check, then the relevant SOP must include this check by a second operative.

Key validation and system procedures include the following:

Preparation of standard procedures
Document review
Validation glossary
Critical parameter assessment
GMP criticality and risk analysis
Process validation methodology
Computerized system validation
Preparation of validation plans
Preparation of project and quality plans
Manufacturing data specification

URS preparation
Supplier audit and evaluation
Qualification protocol preparation
Qualification review and reporting
System access security
Backup, archiving, and retrieval
System operation and management
Contingency/recovery planning
System maintenance
Calibration
Periodic review and reporting
Decommissioning

Incorporating these procedures and the resulting documents into the quality management system will afford a single point of control and archive for all validation procedures.

D. GMP Risk and Criticality Assessment

Accepting that adherence to the validation life cycle for computer system applications is in itself a method for minimizing risk, the use of formal GMP risk assessments on new and existing applications enables the risk of noncompliance with regulatory requirements to be monitored and controlled throughout the life cycle. Risk priorities are likely to change throughout the validation life cycle, and consideration should be given during validation planning to undertaking/updating risk assessments at key points throughout the life cycle as application and system detail becomes available.

The assessment should focus on identifying risks to the GMP environment and evaluating the risk likelihood and the severity of impact on the manufacturing process. This will allow risk criticality to be categorized, and together with an evaluation of the probability of detection will enable definition of the action(s) considered necessary to mitigate and monitor each risk. The GMP risk and criticality assessment will assist in identifying the systems and functionality that require validation effort, and will also highlight areas of concern that may attract the attention of the regulatory inspectors. Assessment records complete with the respective system validation rationale should be kept in the validation file.

The initial assessment should be undertaken early in the planning phase and include definition of system boundaries in order to determine and document what systems are to be in the validation program and why. A sitewide inventory should assign each computer system a unique number, descriptive title, and location reference. The main software and hardware components of each system

should be recorded and reference made to the source of quality-related process parameter information.

Each computer system must be evaluated with respect to the functions it performs and the impact on the GMP regulatory environment, thus new systems that need to be validated are identified and existing GMP systems can be confirmed as candidates for a validation status check.

The next risk assessment should be undertaken just prior to issuing the URS, when the process and the user requirements for the system are defined, enabling the affect of system failure, malfunction, or misuse on product quality attributes and the safe operation of the system to be evaluated. This assessment can be reported as part of the URS review and should identify system requirements that need to be reconsidered.

Further risk assessment in the design phase will allow the detailed operation of the computer system as described in the supplier design specifications to be addressed, and enables criticality ratings to be reviewed against the detailed functions of the system and the SOPs. The assessment will provide documented records to support any update to the risk appraisal.

Such analysis can be complimented during definition and design by consideration and identification of safety, health, and environmental matters and application hazard and operability studies generally undertaken as part of GEP.

System GMP risk assessment reviews can be addressed in the qualification summary reports and the validation report, and updated as part of the periodic review of the system validation status.

E. Software and Hardware Categories

Software and hardware types can influence the system validation rationale, and a strategy for the software and hardware types that may be used should be addressed during validation planning.

The type of software used in a GMP manufacturing computer system can be categorized to provide an indicator of the validation effort required for the computer system. This should be addressed in validation planning, and can be examined and recorded during the supplier audit. Software categories should also be reviewed at the DQ stage, before finalizing the levels and priorities of qualification testing.

It should be noted that complex systems often have layers of software, and one system could exhibit one or more of the software categories identified below:

Operating system software—document version and data communication protocols, and establish extent of use.

Standard firmware (non-user-programmable)—document version, document user configuration and parameters, calibrate, verify operation

Standard off-the-shelf software packages—document version, verify operation

Configurable software packages—validation life cycle with qualification of the hardware and application software

Custom-built software and firmware—validation life cycle with qualification of the hardware and all custom software

The hardware strategy should consider the preferred use of standard hardware components and the potential need for custom-made hardware. The category of hardware components required to meet user and design requirements will provide a guide to the level of hardware specification, design documentation, and development and testing records and will influence qualification activities.

F. Quality-Related Critical Parameters

A fundamental objective of a computer system applied to automate a pharmaceutical GMP operation is to ensure the quality attributes of the drug product are upheld throughout the manufacturing process. It is therefore important that quality-critical parameters are determined and approved early in the validation life cycle. The exercise should be undertaken to a written procedure with base information from the master product/production record file examined and quality-critical parameter values and limits documented and approved for the process and its operation. In addition, the process and instrument diagrams (P&IDs) should be reviewed to confirm the measurement and control components that have a direct impact on the quality-critical parameters and data. This exercise should be carried out by an assessment team made up of user representatives with detailed knowledge of both the computer system application and process, and with responsibility for product quality, system operational use, maintenance, and project implementation. This exercise may be conducted as part of an initial hazard and operability study (HAZOP) and needs to confirm the quality-related critical parameters for use in (or referenced by) the computer control system URS.

The parameters should be reviewed to determine their function (e.g., GMP, safety, environmental, or process control). Applicability of any of the following conditions to a parameter (or data or function) will provide an indication of its GMP impact:

The parameter is used to demonstrate compliance with the process.

The normal operation or control of the parameter has a direct impact on product quality attributes.

Failure or alarm of the parameter will have a direct impact on product quality attributes.

The parameter is recorded as part of the batch record, lot release record, or any other GMP regulatory documentation.

The parameter controls critical process equipment or elements that may impact product quality attributes independent of the computer system.

The parameter is used to provide or maintain a critical operation of the computer system.

As applicable, quality-related critical data should be identified in the loop/instrument schedule and system input/output (I/O) listings.

It is opportune at this point to document the GMP electronic raw data that need to be collected by or through the computer system. This will be used to support the validation rationale and influence the extent of qualification testing. It will also identify candidate data for electronic records and electronic signature compliance and help distinguish between electronic raw data and transient electronic data.

Approved critical parameters and data are not open to interpretation at any time throughout the system validation life cycle. This is particularly important where design and development activities are not directly controlled by the pharmaceutical manufacturer.

G. Validation Master Plan

As with all validation life-cycle documents, a validation plan is a formal document produced by the pharmaceutical manufacturer. The plan should require that all validation documentation is under a strict document control procedure, with issue and revision of documents controlled by means of an approval table, identifying the name, signature, date, and level of authority of the signatory.

A validation plan should describe the purpose and level of the plan and must be consistent with established policies and the GMP risk and criticality analysis. The document must be approved and state the period after which the plan is to be reviewed.

Computer systems that are identified as requiring validation must be included in the site validation master plan. A validation master plan is typically used as a high-level plan for the site or processes and systems that make up the facility GMP operations. The plan should outline the scope of the validation program, controls to be adopted, and how activities are to be conducted, documented, reviewed, approved, and reported. Target completion dates should be included for validation work in each area.

It should address and identify procedures for:

Validation strategy (including reference to the respective regulations)

Structure, reference/naming conventions

Location of validation documentation

Description of the facility, products, operations, process equipment

Computer system register
Validation evaluation and rationale
Validation program priorities
Justification for nonvalidated systems
Validation organization/responsibilities
Validation training
Ongoing evaluation: periodic review intervals
Use of project validation plans
Support programs and procedures
Reference documents and definitions

The plan should be reviewed annually (as a minimum) to ensure and record that it is current and that progress is being made against the plan.

H. Project Validation Plan

The project validation plan is for individual projects (including equipment) or systems and is derived from the validation master plan. The project validation plan should be closely linked to the overall project and quality plan.

The validation plan should put forward a reasoned, logical case that completion of the defined activities will be sufficient to deliver the documented evidence that will provide a high degree of assurance that a computer system will consistently meet its predetermined specifications.

A project- or system-specific validation plan should address the following in sufficient detail to form the basis for reporting the validation program:

Description of process/environment
Quality-related critical parameters
Purpose and objectives of the system
Major benefits of the system
Special requirements
Specific training needs
System operating strategy
Related GMP compliance/regulations
Physical and logical boundaries
System GMP risk assessment
System validation rationale
Life-cycle documentation
Assumptions and prerequisites
Limitations and exclusions
Quality-related critical parameters/data
Standard operating procedures
System requirement specification
Supplier and system history

Vendor evaluations and audits
System design, development, build
Software review
Qualifications (DQ, IQ, OQ, and PQ)
Qualification and validation reports
Ongoing evaluation
Problem reporting/resolution
Operational plans
Validation file
Internal audits
Support programs/procedures
Reference documents
Authorities/responsibilities
Resource plans and target end dates

The project validation plan is a live document that should be reviewed against each life-cycle step and any other validation milestones (as a minimum). Any changes to the plan should be identified on a revision history section within the document. The plan should be retained in the validation file and should be easily accessible.

For each system validation project the validation team must be identified and would typically consist of designated personnel (normally identified by job function at this stage) that will be responsible for the provision, review, and approval of all validation documents and implementation of the qualification testing.

As applicable, the project engineering contractor and the system supplier/integrator can expect to participate on the project validation team at the appropriate time. The purchasing/contracts groups may also be involved and play a key role in administering contractual validation activities and documentation.

In the case of a computer system applied to a live manufacturing process and integral with plant equipment and the process itself, the project validation plan should specify the relationship of the computer system qualification activities and documentation with that of the corresponding plant equipment qualification and process validation. Indeed, the qualification activities and documentation of these elements of a computerized operation are sometimes combined.

Execution of the project validation plan will provide control and full documentation of the validation.

I. Project and Quality Planning

In the majority of cases, the application of a computer system to pharmaceutical manufacturing is part of a capital investment involving other items of production plant equipment and a wide range of contracted design, installation, and commissioning activities carried out by appropriate engineering disciplines.

The overall project itself requires formally structured planning and control in addition to the validation plans for the computerized operation. To provide this, a project and quality plan from the pharmaceutical manufacturer (or its nominated main contractor) is normally developed as a separate and complimentary document and needs to overview all activities, resources, standards, and procedures required for the project. The plan should define project-execution procedures, quality management procedures, engineering standards, project program, and project organization (with authorities and reporting responsibilities), and reference the project validation plan. There are instances in which the project and quality plan and the project validation plan can be combined into one document.

J. Supplier Project and Quality Plan

As part of the supply contract each supplier or subcontractor needs to provide a corresponding project and quality plan to identify and outline the procedures, standards, organization, and resources to be used to align with the requirements of the pharmaceutical manufacturer's project. The contractors and suppliers involved with GMP work should reference the project validation plan and identify the specific requirements that are to be addressed to ensure the appropriate level of documentation in support of the pharmaceutical manufacturer's validation program.

Project and quality planning by each company is important for multigroup projects, as it enables all those involved in the project—pharmaceutical manufacturer, vendor, or third party—to access a formal definition of project standards, schedule, organization, and contracted responsibilities and monitor interaction at all levels. If elements of the contracted work and supply are to be subcontracted the plan must detail how this work is to be controlled and reported. The supplier project and quality plan must be a contractual document agreed upon by the purchaser and supplier and needs to ensure that:

The pharmaceutical manufacturer's quality management system requirements are met at all stages of the project.
The finished product and documentation will meet quality requirements.
Appropriate resource is made available.
Project time scales and budgets will be met.

Measures or criteria for assessing the attainment of quality objectives should be defined as far as possible, together with an overview of the methods to be used for meeting these objectives.

To support the validation program the computer system supplier's plan should identify which supplier procedures are to be followed for:

Document standards and controls
GMP/validation training
System and data security
Development methodology
Software quality assurance
Design specifications
Software development
Software testing
Hardware testing
Software tools
Configuration management
Change control
Subcontractor control
Purchasing
Information requests/project holds
Deviation reporting
Corrective action
Audits (internal and external)
Activity schedule
Allocated resource

Both supplier and customer signatures on the activity schedule can provide a record, for control of the design and development phase of the validation life cycle in support of DQ. The activity schedule can also be used to identify tasks that require input from the pharmaceutical manufacturer.

Task verification should be to the supplier's standard specifications or procedures.

The supplier needs to ensure that:

The phase objectives are defined and documented.
Applicable regulatory requirements are identified and documented.
Risks associated with the phase are analyzed and documented.
All phase inputs are defined and documented.
All phase outputs meet acceptance criteria for forwarding to the subsequent phase.
Critical characteristics are identified and documented.
Activities conform to the appropriate development practices and conventions.

In summary, the planning phase of the validation life cycle encompasses all the up-front preparation activities and documentation, including:

Validation policy and plans
GMP/validation training
Validation procedures

GMP criticality and risk assessment
Validation rationales
Quality-related critical parameters and data
Project and quality plans

It is imperative that these are in place to support the validation life-cycle activities that follow.

V. REQUIREMENTS DEFINITION

A. User Requirement Specification

The success of a validation program depends initially on the provision and understanding of a formal written definition of the system requirements. The purpose of this URS is to:

Provide sufficient detail to the supplier to produce a cost, resource, and time estimate to engineer and document the computer system within a validation life cycle
Provide information for the system supplier's functional design specification (FDS)
Provide an unambiguous and commonly understood operational and interface listing of functional and system requirements, which can be tested during PQ
Identify all manufacturing design data, including quality-related critical parameters and data for system design and testing
Identify the project documentation (and task responsibilities) to support the validation program

It should be recognized that the URS is the base document for developing and testing the computer system and needs to provide clearly defined and measurable requirements. Authorities and responsibilities for provision of information for the URS must be stated in the project validation plan.

The computer system URS needs to describe the levels of functionality and operability required from the computer system, its application, and the location with regard to the process. Definition of approved and accurate manufacturing and process data is a key objective of the URS and is essential in order for the computer system supplier or integrator to fully understand and develop the computer application and to engineer the field instrumentation and electrical controls. This must include the quality-related critical parameters that are fundamental in determining and ensuring the satisfactory quality of a drug product. Parameters, data, and functions that are necessary to uphold GMP must always be considered as firm requirements and candidates for validation.

It may not be possible or necessary to define all engineering parameters and data on issue of the URS. In such cases the URS should document when the information will be available and provide anticipated ranges for preliminary costing and design purposes. Any such interim action must be strictly controlled and reviewed before detailed design commences.

Quality-related critical parameters, data, and functions are essential for specification and contract considerations, system design and development, qualification testing of the computer system, and PQ for the validation of the process. GMP-related system requirements need to be traceable throughout the specification, design, development, testing, and operation of a system. This can readily be achieved by having a "traceability matrix" that will identify corresponding sections and data in the key life-cycle documents.

For the process measurement and control instrumentation the loop schedule enables allocation of a unique identifier (tag number) to each instrument used in the operation of the plant. This will allow application details to be added to the schedule (e.g., range, accuracy, set-point tolerance, signal type, description, location and any other information thought necessary to provide a clear understanding of the requirements for each instrument).

It should be noted that not all parameters that are critical to the manufacturing process are critical with regard to product quality; some parameters may be designated critical for process performance, safety, health, or environmental reasons. Because of the nature and importance of these other critical parameters, it is usual for pharmaceutical manufacturers to consider them under the validation program.

For purposes of documenting criticality of all instruments and loops the following categories may be used:

Product critical instrument—where failure may have a direct effect on product quality (normally aligning with the defined quality-related critical parameters)

Process/system critical instrument—where failure may have a direct effect on process or system performance without affecting final product quality or safety.

Safety/environmental critical instrument—where failure may have direct effect on safety/environment

Noncritical instrument—where failure is determined to have no effect on product quality, process/system performance, safety, or the environment.

(The criticality designated to each instrument will form the basis for the calibration rationale and calibration frequency for the system instrumentation and regulating devices. For quality-related critical parameters the range and limits must be accommodated by the instrument calibration accuracy and failure limits.)

It must be made clear that the GMP quality-critical parameters and data are not open to interpretation and must be controlled throughout all life-cycle activities and clearly identified throughout the validation documentation. This is particularly important for parameters and data that need to be controlled by restricted access during the design and development phases and also during operation of the computer system.

Another key objective of the URS is to identify the document deliverables to support the validation program and the responsibilities for provision and management of this documentation during the project.

B. Structure and Content of the User Equipment Specification

The URS can contain a large number of requirements and should therefore be structured in a way that will permit easy access to information. The requirement specification must be formally reviewed and approved by the pharmaceutical manufacturer. A number of general guidelines apply to this specification (and all validation life-cycle documents).

Requirements should be defined precisely; vague statements, ambiguity, and jargon should therefore be avoided. The use of diagrams is often useful. The scope for readers to make assumptions or misinterpret should be minimized.

Each requirement statement should have a unique reference.

Requirement statements should not be duplicated.

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, as PQ test procedures are to be derived from the user requirements.

Where applicable, mandatory requirements should be distinguished from desirable features.

Considering the availability and content of the manufacturing design data and the potential document revisions and change control for large or complex applications, it is sometimes advantageous to compile and issue the operation-specific manufacturing design data as a separate specification document appended to or referenced by the URS.

Whatever the format, the URS for a GMP computer control system application will typically address the following:

Scope of system supply

Project objectives

Regulatory requirements

Process overview
System boundaries
Operational considerations
Manufacturing design data
Instrument application data
Data records
System functions
System software
System hardware and peripherals
System interfaces
Environmental conditions
Access security
Diagnostics
System availability
Safety
Test and calibration
Quality procedures
Software development life cycle
Documentation requirements
Training
O & M manuals
Engineering/installation standards
Ongoing support
Warranty
Delivery/commercial requirements

Newly sanctioned systems will require compliance with regulations for GMP electronic records and electronic signatures, and definition of the functionality required will need to be included.

It is recommended that wherever possible the structure of the URS be used as the basis for the presentation format of the FDS and hardware and software design specifications; this helps ensure design decisions are auditable back to the source requirement. Traceability should also be carried forward to the qualification test procedures, where it can link each test and qualification acceptance criterion directly to a specific requirement.

Using a "cross-reference matrix" for traceability of parameters, data, and functions throughout the life-cycle documents provides a valuable control and revision mechanism, and will assist document review and change control by providing a document audit trail for the validation program.

It is advisable to start compiling the matrix on approval of the URS. The exercise can also be used as a check on the key requirements itemized during the initial GMP risk assessment and to provide focus for developing initial quali-

fication test plans. The status of the traceability matrix should be recorded as part of each qualification summary report and kept in the validation file.

The URS is a "live" document (or set of documents) and may require revising at various points in the project. It should be retained in the validation file and should be easily accessible. Any revisions must be carried out under a strict change control procedure.

Once reviewed and approved internally, the URS is issued to prospective suppliers as part of the tender document set so that detailed quotations for the system application can be obtained. The contractual status of the URS and its importance to the validation program should be made clear to the supplier.

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

Clarifies technical, quality, and documentation requirements to the vendor(s)

Enables the pharmaceutical manufacturer to assess the technical, regulatory, and commercial compliance (or otherwise) of submitted bids against a formal specification

Ensures the basis of a structured approach to the presentation of information that can be carried forward into the specifications produced during the system development phase

Provides a basis for testing and test acceptance criteria

It is recognized that the URS may be superseded by the FDS as the definitive specification for system design. The URS, however, remains the technical and operations statement of user requirements and must be maintained under change control as an up-to-date document throughout the life of the system. The URS also remains the base document against which PQ is verified, and once the URS is approved a PQ test plan can be generated.

VI. SUPPLIER SELECTION

Manufacturing process control and automation systems can be divided into two main categories [3].

Stand-alone systems. Multiloop controller(s) or programmable logic controllers (PLC) typically used to control part of a process, and larger supervisory control and data acquisition (SCADA) systems/distributed control systems (DCS) used to control the process or service as a whole (e.g., bulk primary production plant, building management systems). These self-contained systems are a component of an automated manu-

facturing process application and are usually developed and delivered as free-standing computer systems by the system supplier separate to the process equipment for connection to the associated "field" instrumentation/regulating devices and, as applicable, to each other.

Embedded systems. Smaller microprocessor-based systems, such as a PLC or PC, with the sole purpose of controlling and/or monitoring particular manufacturing equipment. They are usually developed and delivered by the equipment supplier as an integral component of the process equipment or package plant, (e.g., filling machine, packaging machine).

For both embedded and stand-alone systems the supplier must adopt a life-cycle approach to system design and development to provide a level of documentation that can be used to support the qualification phases and requirements traceability from specification through to testing. This will also to support effective validation at minimum cost.

A. Selection Criteria

Pharmaceutical manufacturers expect the computer system supplier or integrator to understand the needs and constraints of the GMP environment. The fundamental requirement is for the system supplier to ensure that no assumptions are made with respect to the accuracy and dependability of the system. For this, the following need to be addressed:

Design for consistently accurate and reliable operation

Reduce exposure to loss of expertise and knowledge by documenting system application, design, development testing, problem resolution, and enhancements

Minimize risk to system design, development, operation, and maintenance by conducting and recording these activities to approved written procedures

Selection of the computer system and system supplier involves evaluation of a supplier's development and project working methods, and also initial evaluation of the basic system software and hardware functionality with regard to GMP application.

A supplier will need to demonstrate structured working methods with full and auditable system documentation. The chosen supplier will also be expected to provide qualified and trained resource with appropriate knowledge of validation methodology and experience in providing solutions for GMP-regulated applications.

Suppliers with system development and project execution procedures in line with validation life-cycle requirements are well placed to deliver the appropriate level of validation support documentation. The existence of supplier test

procedures that cover system acceptance testing and support qualification testing will streamline the validation. Suppliers that can analyze how their system functionality aligns with GMP are in a good position to directly assist with key activities within the validation program (e.g., GMP risk and criticality assessment and maintenance).

It is recognized that an in-place and in-use quality management system certified to (or in line with) the ISO series of quality standards is key to supporting system validation goals. In particular, certification to the TickIT Software Quality Management System [11], with its emphasis on software development to ISO guidelines, can be a distinct advantage. The supplier will need to demonstrate a documented process for planning, implementing, controlling, tracking, reviewing, and reporting all project activities in a structured and consistent manner.

Evaluation and selection criteria for the system software will depend upon the type of software being considered. For standard software, such as the operating system or a canned or commercial off-the-shelf configurable package, a history of satisfactory use is a major consideration. The number of installations 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, may provide adequate evidence that a program is structurally sound.

If software is to be developed or custom-configured for the application, the supplier's software quality assurance program would be a key factor in indicating the ability of the supplier to provide an acceptable system. For a newly developed system consideration should be given to examining the design, development, and testing methods and records of the operating system software to the same level as for application-specific software. The computer system supplier should be able to demonstrate data integrity within the system and associated interfaces and networks, using proven data communication protocols and onboard diagnostics that monitor and record accurate data transfer.

Hardware evaluation tends to be less complex than software evaluation, and unless hardware is being designed and built specifically for the application it will generally comprise standard components with defined performance detail that can be evaluated relative to the functional requirements and operational specifications. This also applies to the measurement and control instrumentation.

The evaluation should also examine the ease of calibration and self-documentation of both the computer system and associated measurement and control instrumentation, along with the availability of replacement parts and service support for the expected lifetime of the system application.

The history of the computer system in similar applications should also be explored to determine evidence of system durability, reliability, repeatability, and accuracy.

B. Vendor Evaluation

Initially potential suppliers can be sent a postal questionnaire that requests information on the company, the services provided, resources, system development expertise and range of experience, customers they have supplied, and maintenance support.

Two main areas should be addressed, and the vendor records may need to be examined during the supplier audit.

- The methodology and records for design and development of system source code (operating system level), including version control and management and access availability.
- The procedures used to design and develop project-specific application software, including version control and management, the documentation provided, and backup copy availability.

Responses to the questionnaire should be formally reviewed and a report produced that highlights any perceived areas of weakness or points for further investigation. From a formal review of the responses, those suppliers who are considered most suitable can progress to the next stage of evaluation.

C. Inquiry and Quotation

The tendering process is primarily associated with the overall engineering and commercial considerations but is important to the validation program in that it provides the means to:

- Clearly define what is required from the computer system supplier
- Identify initial and collective interpretation issues that need to be clarified
- Capture the initial supplier documentation describing how they intend to meet the user requirements
- Introduce into the selection process the supplier evaluation and audit findings regarding GMP and validation requirements for personnel qualifications, working methods, level of documentation, and in-built system functionality

Depending on the contractual approach, the responsibility for the provision, design, and testing of the computer system may be separate from that for the application engineering, provision, design, and testing of measurement and control instrumentation (and associated "field" equipment; e.g., cabinets and cabling).

The tender package documentation needs to provide all the elements necessary to define the project, and typically includes the project validation plan, a detailed scope of work, the URS, the documentation deliverables, and the associated commercial documentation.

The pharmaceutical manufacturer should request all technical information relevant to the tender in a standard form, and the vendor should be asked to detail its solution by referencing specific inquiry document sections, clearly identifying any requirement that cannot be met.

The main tender document submitted by a vendor will be the FDS, and this needs to include traceability to all specified user requirements. Vendors should also be requested to outline a project and quality plan to identify how they would carry out the project.

The quotations are to be formally evaluated by the pharmaceutical manufacturer with the purpose of selecting the proposal that best meets requirements and fully supports the pharmaceutical manufacturer's validation program. Quotation evaluation should involve the user representation necessary to ensure that quality, validation, GMP risk, production, technical, maintenance, commercial, and safety and environmental requirements are properly addressed.

The quotation should be evaluated methodically against the following criteria and each evaluation meeting recorded:

Capability of a supplier to meet all defined project and support requirements
Alignment of proposed system FDS with the URS
System life-cycle development methodology and documentation
Costs of proposed system
Delivery dates and program

D. Supplier Audit

Unless a recent and similarly focused formal audit has already been undertaken, the pharmaceutical manufacturer should conduct a detailed audit at the premises of the potential supplier(s) to examine the in-place methods and records reported by the vendor prequalification and any submitted quotation. Audits may be undertaken before and/or after the quotation stage.

A supplier needs to recognize the importance of this examination in providing a documented record for the pharmaceutical manufacturer's validation program and be prepared to fully support the audit (and any follow-up activities) in a timely manner. Guidance on computer system supplier audit issues is available in the GAMP guide [3] and from the PDA Technical Report 32 [12]. With most system suppliers operating under ISO-certified or similar quality systems, training afforded by appropriate courses on the TickIT Guide [11] will also benefit software audits. At a minimum, the following considerations of a supplier's operation would need be examined:

Company finances and stability
Management commitment
Organization

Quality management system
Professional affiliations
Confidentiality
Resource availability/qualifications
GMP application knowledge
Training program
System(s) availability
System life planning/migration
System engineering procedures
Project procedures
Procurement procedures
Subcontractor control
Production procedures
System "build" security
Site installation/testing procedures
Handover and final documentation
System operating procedures
Calibration/maintenance procedures
Maintenance support and equipment
Document control
Change control
Internal audits
Review and approval process
Configuration management
Contingency/recovery procedure

As appropriate, the following quality assurance practices and records applicable to the operating system software, application-specific software, and hardware should be reviewed by the pharmaceutical manufacturer (or its nominated representative):

Operating system code availability
Software/hardware specifications
Software/hardware design practices
Product design records
Program coding standards
System development records
System test records
Programming tools
Control of nonoperational software
Removal of "dead code"
Deviation analysis/corrective action
Virus detection and protection

Software release
Master copy and backup
Version control
Software replication
Problem reporting/resolution
Fault notification to customers

To automate operation of pharmaceutical manufacturing processes, the computer software in many instances becomes the "operating procedure," and thus the following in-built functionality and performance of the computer system itself should also be examined to ensure alignment with GMP application:

System controls
Access security (SW and HW)
Data integrity (data transfer)
Electronic record/signature
Accuracy
Repeatability
Self-documentation
In-built diagnostics

An audit report will serve as the formal record of the audit and its findings, and is a major input into selecting the supplier and determining any necessary corrective action. To complete the quotation review exercise the pharmaceutical manufacturer (or its main contractor) should produce a formal report that summarizes the quotation compliance, the key points of the audit report, and the main benefits of each system. The chosen supplier and reasons for the supplier selection should be clearly stated.

A review of the GMP risk implications should be undertaken at this time and may be included as a section of the report.

E. Award of Contract

Any revisions that have been agreed upon by the pharmaceutical manufacturer and the selected supplier must be included in the tender package documents and quotation. Any revisions to the URS must be implemented under the pharmaceutical manufacturer's change control procedure.

A formal agreement that references all relevant tender documents and clearly identifies responsibilities and document deliverables should be prepared by the pharmaceutical manufacturer. The purchase order should include the final agreement and identify any associated contractual documentation. A copy of the signed final agreement and purchase order should be retained in the pharmaceutical manufacturer's validation file, together with evaluation records applicable

to the selection of the chosen supplier. The latter should include the initial list of prospective system suppliers, and the prequalification, audit, and quotation related to the selected supplier.

The computer system supplier's detailed project and quality plan incorporating the procedures for software quality assurance should be one of the first contracted deliverables, if not already submitted as part of the quotation or requested during precontract discussions.

At this point for both the project schedule and the validation program the emphasis is on work activities that are contracted to the supplier(s) for system design and development and aimed at fulfilling the agreed-upon FDS. The majority of this is work is normally conducted at the supplier's (or engineering contractor's) premises.

VII. DESIGN AND DEVELOPMENT

The design, development, and "system build" phases need to deliver computer systems and services in a manner that facilitates effective and efficient system validation, operation, maintenance, modification, and upgrade. This applies to both stand-alone and embedded process control computer systems (see Sec. VI).

Design, development, and system build is normally a period of intense activity, in which a supplier will be involved in life-cycle activities and will need to provide a set of auditable design and development documentation to support the validation program. For this, the entire design and development process should be carried out to written and approved procedures, and all design, development, testing, and verification activities should be documented and approved in order to provide a level of computer system documentation that can be used to support the pharmaceutical manufacturer's life-cycle qualification activities.

The supplier's design, development, and system-build activities should be based on a set of top-down design specifications and a corresponding set of development test procedures and records, with all work undertaken to the supplier project and quality plan and in line with the pharmaceutical manufacturer's project validation plan. The documentation for design, development (including development testing), and system build must be progressed through an agreed-upon document control system, with approved documents under strict revision and change control.

A. Functional Design Specification

The overall design intentions for the computer system should be defined in an FDS which is normally written by the supplier and must describe how the intended system will meet the customer's application requirements. Once the FDS

is produced there should be a formal verification that it addresses the functions set out in the URS. (See Sec. V.)

The FDS needs to clearly identify any nonconformance with the URS, giving the reasons for any divergence. Similarly, any system function or software that is an integral part of the system on offer and would exist within the system but not be utilized for the application must be identified, complete with proposals of how the function or software can be made inoperative or protected from misuse. The pharmaceutical manufacturer must examine all such issues for operational and GMP impact and if applicable the URS must be formally updated under change control. If not detected at this stage, omissions and misinterpretations will inevitably mean modification at a later date, with the risk of delays and budgetary overruns.

When the FDS is approved it must be subject to formal change control by the supplier for any subsequent amendments. Change control should also be applied to any dependent documents.

The FDS must include all measurable or determinable parameters that may affect system performance and identify the source of supply of both hardware and software. The FDS needs to address each user requirement, defining the following:

- The system hardware and software architecture
- Data flows and records
- The functions to be performed by the system and all normal operating modes
- The manufacturing data on which the system will operate, and connections to the manufacturing process through the measurement and control instrumentation
- How the integrity of quality-related critical process parameters and data will be maintained throughout design, development, and acceptance testing and within the system in its operational use
- The system interfaces; i.e., the operator interface and interfaces to other systems and equipment
- Testing and diagnostic provisions
- All nonfunctional considerations related to the system use

For each function of the system the following needs to be a addressed:

- Objective of the function
- Use of the function
- Interface to other functions
- Performance and limitations of the function in terms of accuracy, resolution, and response time
- Safety and security, including access restrictions, time-outs, data recovery, and loss of services

By defining each function in this manner the framework of the respective test procedure exists as each function has to be tested against these criteria.

To support requirements and critical parameter traceability the FDS should, where possible, adopt the format of the URS. (See Secs. V and VI.) It is important that these primary corresponding specifications are fully understood by both the user and the supplier and are formally reviewed and approved before the supplier prepares the design specifications for hardware, software, and the control and monitoring instrumentation and regulating devices.

In summary, the life-cycle objectives of the FDS are as follows:

To define how the supplier's system will meet the needs of the pharmaceutical manufacturer as detailed in the URS (i.e., the FDS is the physical mapping of the supplier's system onto the URS)

To enable the pharmaceutical manufacturer to examine the feasibility of the manner in which the supplier will meet the requirements stated in the URS

To allow the pharmaceutical manufacturer to understand the extent to which the system as defined meets the requirements of the URS

To ensure a structured approach to the presentation of information that can be referenced to the URS and carried forward into the software and hardware design specifications

To define functional design requirements on which to base the detailed software and hardware design specifications

To provide the base document for OQ testing

The FDS will also form the basis for contractual acceptance testing, both at the supplier's premises (factory acceptance test, FAT) and on delivery to the site (site acceptance test, SAT). With suitably compiled test procedures these "traditional" contractual acceptance tests may be incorporated with the qualification testing required by the validation life cycle.

To address this level of testing the FDS should outline the calibration, testing, and verification needs of the computer system to ensure conformance with the manufacturing design data, and in particular the critical process parameters. For this the FDS needs to consider:

Review of calculations
Testing across full operating ranges
Testing at the range boundaries
Calibration of connected instruments
Testing of alarms/interlocks/sequences
Electronic data records
Conditions and equipment
Record of test results

B. System Design Specifications

System design uses a top-down approach with an appropriate level of design specifications to detail how the system hardware and software will be built to meet the application design requirements defined by the FDS.

System design specifications will be used by the supplier as working documents during the design, development, integration, and "build" of the system, and after qualification of the system as support documentation by those responsible for the maintenance and future enhancement of the system.

The system design activities include:

- The detailed design and provision of computer system hardware and software to meet the requirements of the FDS
- The detailed application engineering and design for measurement and control instrumentation, interconnecting cabling/tubing, and the associated installation, to meet the manufacturing process specifications

Any divergence between the system design specifications and the FDS should be clearly identified by the supplier. The pharmaceutical manufacturer should review any nonconformance with the supplier, and to ensure consistency the outcome should be reflected in controlled changes to the preceding requirement specifications and/or system design specification.

The pharmaceutical manufacturer should consider its role with regard to system design documents in light of the experience available to it. It may not be appropriate to approve system design specifications, but may be appropriate to provide comment on the level of information. It should be noted that some form of diagrammatic representation can improve understanding of system design specifics.

C. Hardware Design Specification

The hardware design specification must describe the hardware that will make up the computer system and the hardware interfaces. The defined hardware should be traceable back to statements in the FDS. Once the hardware design specification is produced and approved it is possible to generate a hardware test specification.

The objectives of the hardware design specification are as follows:

- To define the constituent hardware components of the system, how they intercommunicate and what constraints are applied to them
- To define any communication to external systems and measurement and control instrumentation, and the associated hardware requirements
- To enable the pharmaceutical manufacturer to determine the implementation strategy of the supplier

To enable the supplier to demonstrate the correctness and completeness of the hardware design with the FDS
To allow the pharmaceutical manufacturer to understand and compare the hardware design and traceability to the FDS
To provide input to the hardware test specifications
To ensure a structured approach to the presentation of information that can be carried forward into the hardware test specification

The structure of the hardware design specification should be such as to facilitate comparison with the FDS.

D. Software Design Specification

For GMP applications the software development must be based on a fully documented and structured design and formally reviewed to ensure that it is reliable, safe, testable, and maintainable. A modular approach to software design with annotated documentation will provide a better understanding of the system software throughout the relevant life-cycle activities and also during regulatory inspection. Use of standard software should be considered whenever possible.

The software design specification is written by the system supplier and must identify how the supplier intends to provide system software under a software quality assurance plan. The design specification must describe the subsystem software that will make up the computer system software and subsystem interfaces to implement the aims set out in the FDS. Each subsystem should be traceable back to statements in the FDS.

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 software definition and testing correspond.

The software design specification has the following objectives:

To define the constituent software components of the system, how they intercommunicate and what constraints are applied to them
To enable the pharmaceutical manufacturer to determine the implementation strategy of the supplier
To allow the pharmaceutical manufacturer to ensure the correctness and completeness of the software design through traceability to the FDS
To provide input to the system integration test specification
To ensure a structured approach to the presentation of information that can be carried forward into the software test specifications
To ensure a structured approach to the presentation of information that can be carried forward, as applicable, into the software module design specifications produced later in the system design

The structure of the software design specification should be similar to that of the FDS to facilitate checking between the two documents.

E. Software Module Design Specification

A software module design specification shall be produced for each software subsystem identified in the software design specification. The software module design specification must document how module design will be implemented and must contain enough information to enable coding of the modules to proceed.

The software module design specification has the following objectives:

To define the implementation of individual modules—how they communicate within the subsystem software and what constraints are applied to them

To enable the pharmaceutical manufacturer to determine the implementation strategy of the supplier

To allow the pharmaceutical manufacturer to ensure the correctness and completeness of the software implementation through traceability to the software design specification

To provide input to the software module test specifications

To ensure a structured approach to the presentation of information that can be carried forward into the software module test specifications

The structure of the software module design specification should be similar to that of the software design specification to facilitate checking between the two documents. Once the software module design specification is produced and approved it is possible to generate a software module test specification.

F. Instrumentation Application Engineering

The design of control and monitoring instrumentation and regulating devices should be based on an established document management system that enables preparation to be formally approved, implemented, recorded, and audited. Typical contents and document deliverables of an integrated engineering documentation system are as follows:

Drawing register
Loop schedule
Instrument data sheets
Instrument loop schematics
Logic and interlock diagrams
Wiring diagrams

Pneumatic hookups
Process connection drawings
Instrument/electrical interface
Earthing schedule and drawings
Cable/tubing routing drawings
Cable and termination schedules
Cabinet/rack layout
Control room layout
Operator console/station(s)
Field panel and junction box layouts
Label schedule
Instrument installation specification

Application engineering and design for measurement and control instrumentation is an interactive process that is centered on a loop schedule normally generated from an approved set of P&IDs and approved manufacturing process data. Because of the interrelationship between the various types of instrument design documentation and the sharing of design information, many of the documents are produced in parallel.

All manufacturing process data should be approved by the pharmaceutical manufacturer end-user and quality assurance groups and be specified as manufacturing design data, including critical process parameters and data, as part of the URS.

The loop schedule and instrument data sheets [9] are key documents that enable process data to be recorded in a manner that brings together the computer system and the process to be controlled and monitored.

G. Loop Schedule

The loop schedule should list all in-line and associated instrumentation for the process application. For each instrument, a typical loop schedule will be developed to provide the following information:

Unique tag number
Service/duty description
Equipment description/type
Alarm action
Interlock action
Location
Manufacturer
Purchase/requisition number
P&ID reference
Specification or data sheet number
Electrical hook-up drawing number

Pneumatic hook-up drawing number
Process hookup drawing number
Control system I/O signal and address

H. Instrument Data Specification Sheets

These are generally standard preformatted documents that provide the technical specification and design data for each instrument on the loop schedule, and are primarily used for purchasing the equipment and the basis for calibration.

Each instrument specification would include instrument, process, and environmental information to enable correct application of each instrument to the manufacturing process. For each instrument and under a unique tag number all the physical, technical, installation, operating conditions, and service requirements are to be documented and must include:

Range of instrument and manufacturer's accuracy
Materials of construction, especially of process contact (wetted) parts
Process connection details (e.g., chemical seals, capillary lengths, flange rating)
Control characteristics (as applicable)
Process media reference
Working range (of the measured process variable)
Control set points, alarm, and interlock switch points (as applicable)
Engineering range and signal type/level
Operating/calibration tolerances
Fail-safe mode

Each data sheet should also identify the expected support documentation and the number required, for example:

Factory calibration certificates
Testing/calibration equipment identification (e.g., traceable to national standards)
Manufacturers' operation and maintenance manuals
Approval certificates for EMC/RFI/hazardous areas
Layout drawings showing overall dimensions
Electrical schematic wiring and/or pneumatic connection diagrams
Nonlinear range/calibration charts
Valve sizing calculations

I. Software and Hardware Development

The development for the computer system is based on the design specifications and once the system design specifications for the application have been agreed upon the computer system development and build can commence.

This phase of the supplier's work will be conducted according to the agreed-upon project and quality plan using the supplier's approved procedures, and will involve:

Provision of system hardware, software, and associated instrumentation that are part of the contracted supply
Application software development, including development testing
System assembly
Hardwiring of components
Documentation preparation

J. Software Code and Configuration Review

The development phase needs to accommodate a software code/configuration review process to:

Provide a high level of confidence that the software code or configuration meets the defined operational and technical requirements of the system design specifications and the URS
Ensure that the software code or configuration is to a standard that will ensure clear understanding and support maintenance and modification of the software throughout the system validation life cycle

The pharmaceutical manufacturer, or its designated representative, would normally conduct software review(s) prior to the supplier's software development testing in order to reduce the potential of retesting.

For the review(s) to be effective the reviewer must have knowledge of the software techniques and the system application. The review should be carried out in accordance with a written procedure and the findings should be documented. The scope and degree of software examination will need to be decided and justified, with consideration as to whether a single review conducted on completion of the software development or a series of reviews throughout the software development is the most appropriate approach for the software being developed.

A decision not to perform the review (e.g., evidence that code is developed under a quality system and formal reviews have already been conducted and reported) should be documented in the project validation plan, complete with the rationale. It is recognized that under its software quality assurance program the supplier may conduct similar examination of the software using only internal resource. Considering GMP implications, the pharmaceutical manufacturer would normally require that the software designer or programmer does not carry out any software review in isolation.

A variety of methods have been developed to review software (e.g., inspections, walkthrough, and audit). Flow charts graphically representing data flow and software module architecture will clearly aid the review, particularly when verifying design requirements.

The review needs to determine:

Adherence to specified software standards and practices
Adequate annotation that identifies the software, clarifies data and variables, and clearly describes operations to be performed
Adherence to software design specifications for the application
Possible coding errors
Presence of any "dead" or "unused" software (with the agreed resulting action)

A software review will typically cover software record availability and content, any previous review findings, support documentation, configuration, and change control records. First, the review should investigate adherence to suitable documented software practices for consistency in approach, complexity control, terminology, readability, maintainability, version control, and change control. Second, key areas of software should be identified with due consideration of the system complexity and size, programming competence, system history, operating environment issues, and GMP criticality. For this key software the reviewer needs to examine the following in relation to the design specifications and the predefined quality-related critical parameters, data, and functions:

The logic flow of data
Definition and handling of variables and I/O
Control algorithms and formulae
Coded/configured calculations
Allocation and handling of alarms, events, and messages
Process sequencing
Process and safety interlocks
Content of electronic data records, logs, and reports
Information transfer
Error handling
Interfaces with other systems
Start-up and failure recovery

The operability of the system must also be examined so that there is confidence that the configuration ensures unused system functionality is deselected and cannot be used.

A report should overview the software review findings and append or reference complete sets of annotated software listings resulting from the review.

Where the supplier withholds software listings an access agreement should be established.

The report should document any corrective action or change that is required to make the software acceptable. Corrective action plans should document responsibilities and the rectification date, and where applicable record the change control reference number. Resolution of any problems should be reported under the DQ.

K. Software and Hardware Development Testing

During system development and build the supplier will normally be responsible for all software and hardware development tests and reports, with the pharmaceutical manufacturer involved as agreed upon under the contract. Development test specifications are to be used to demonstrate that the developed software and hardware provides the functionality and operation as defined in the system design specifications.

In many instances operating system software has already been developed and is offered as a fundamental part of the computer system ready for application software to be developed or configured. In such cases it is prudent to establish the existence of the respective software quality assurance plans and procedures and the design, development, and testing records. Identification and examination of this documentation can be conducted and recorded as part of the supplier audit. (See Sec. VI.)

Development tests must be derived from and traceable to statements in the respective design specification, and hence will be traceable to the FDS and URS. Tests for each requirement should be prepared on completion of each design specification to help ensure all matters are addressed.

Testing of application software should include both structural verification and functional testing. Structural verification of software takes into account the internal mechanism of a system or component, and is to ensure that each program statement is made to execute and perform its intended function. Functional testing focuses on outputs generated in response to selected inputs and execution conditions, and is conducted to evaluate the compliance of a system or component with specified functional requirements and corresponding predicted results. For both forms of testing 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.

All levels of development testing for the computer system must be fully documented and provide test records in the form of approved test procedures, signed-off test result sheets, and reports. For system parameters, data, and functions that are critical to product quality and GMP compliance it is beneficial that the test procedures align with qualification test requirements, and record

tests and calibrations against predefined expected results and acceptance criteria. This will allow supplier development testing records to be considered for use during the life-cycle qualifications.

Software and hardware testing starts during the development phase with a bottom-up approach, software module, and hardware tests need to verify that the implementation of the design for each software or hardware element is complete and correct. Integration testing in which software elements are combined and tested as a complete application program should where possible be conducted using the actual computer hardware. These tests will include all system interfacing, networking, and field connection requirements, and are part of the supplier's in-house test activities to ensure computer system readiness for acceptance testing.

Development test specifications include the following:

Software module test specification—for testing individual software components against the software module specification
Hardware test specification—for testing the hardware components against the hardware design specification
Integration test specification—for testing the software module integration against the software design specification on suitable hardware.

A development test specification should define:

Software and hardware to be tested
Tests to be performed
Data or inputs to be tested
Test method
Expected results
Acceptance criteria
Test and witness personnel
Test location and environment
Test equipment/software required
Test documentation required

A development test specification needs to be prepared by someone with knowledge of the respective design specification but who has not been involved in its implementation. This is to ensure that the testing is not influenced by knowledge of the development.

Each test procedure and resulting test result sheet(s) should be linked by a unique test reference number and be in a logical order, particularly if a series of tests are required for similar items. This ordering method should be clearly explained.

Each test run should be recorded on a separate test result sheet and signed and dated as a minimum by the tester and a test reviewer. All test information should be recorded on the test result sheet, or as necessary on clearly identified

separate sheets attached to the test sheet. The information collected may then be used for summarizing and reviewing the results of the tests.

A development test result sheet should include the following information at a minimum:

Name of software or hardware
Reference number of software or hardware
Version or model number
Type of testing being undertaken
Test equipment/software used
Test reference number
Test-run number
Number of attached sheets
Data or inputs tested
Expected result(s)
Test result(s)
Comments/observations
Time taken for test
Overall test status (pass/fail)

A test is deemed to be successful only if all the acceptance criteria defined in the test procedure have been met. A test review team should be formed that will assess and report on all tests, and any involvement by the pharmaceutical manufacturer should be documented. This team should have final authority on test findings. As required, the test review team should decide where controlled changes are required to specifications and whether or not tests should be rerun. Tests are to be conducted in a logical order, and adverse test results must be resolved before progression to any linked test or the next development phase.

L. Software Release

Supplier software release and replication procedures must ensure that only approved products are available for use by the pharmaceutical manufacturer. It is advisable to have release authority with review groups who are independent of the development team.

Only upon the successful completion of the integration testing and documentation review should product release be authorized. Once an application software program is released, it should be placed under formal configuration/version control, and any revisions must follow the requirements of a change control procedure.

M. System Build

For an embedded system the final assembly of the control system and associated electrical and mechanical components into the manufacturing equipment will

normally precede factory acceptance testing of the automated equipment at the supplier's premises, or may take place in a controlled area of the user's site.

For a stand-alone system the computer system normally undergoes factory acceptance testing at the supplier's premises, and as with associated instrumentation and regulating devices is shipped to the site, inspected, and where applicable is stored and then installed with the manufacturing process/plant equipment.

In both cases, the system build phase is to be performed according to the specifications and assembly drawings of the component manufacturer. Assembled systems using hardware from different sources require verification confirming the compatibility of interconnected hardware components.

N. Acceptance Test Specification

Formal acceptance testing to an agreed-upon specification is to be carried out on the developed software and hardware and for the engineered measurement and control instrumentation. This is intended to prove to the pharmaceutical manufacturer that all components and documentation are available and the system functions as defined in the system specifications. The acceptance test specification should include verifications and tests covering the following:

All hardware and software documented
All operational and control functions of the FDS
All data storage and reporting requisites
All alarm and error reporting functions
All measurement and control instrumentation inspected, calibrated, and installed

The acceptance test specification may contain a large number of tests. It should therefore be structured in a way that will permit simple cross-reference to the functions specified in the FDS, and hence the URS.

The supplier will normally apply GEP in covering the two parts of this contractual acceptance test, namely FAT and SAT. However, and if required by the pharmaceutical manufacturer, it should be possible to structure acceptance testing to include the enhanced level of verification, testing, and documentation that are necessary for the in situ qualification under the validation life cycle.

O. Factory Acceptance Test

This is normally the first stage of system acceptance testing and should be witnessed by the pharmaceutical manufacturer prior to agreement for the system to be delivered to the site. The supplier should ensure that the system can pass the predefined tests prior to the witnessed acceptance testing so as to minimize the risk of any retesting. The supplier may be requested to produce records of

any preparatory testing that was not witnessed by the pharmaceutical manufacturer.

The FAT is normally a contractual acceptance test that serves to ensure that within the limitations of testing available at the supplier's premises the system operates satisfactorily, and for any problems identified during testing has the advantage of being directly resourced and resolved in the development environment. Problems (particularly software-related) carried over or detected on site are invariably more difficult and time-consuming to rectify.

It is also important that the extent of the FAT is maximized. This will reduce the risk of problems arising during the final acceptance tests carried out on site and during system qualification. At this stage any dynamic testing considered for real-time computer process control systems will need to be undertaken utilizing simulation software, which in itself may need to be validated.

A satisfactory FAT report for the computer system also supports DQ by finalizing predelivery testing for the design and development phases of the validation life cycle.

P. Instrument Inspection and Calibration

For the control/monitoring instrumentation, regulating devices, and any associated electrical equipment, predelivery testing and calibration is normally the responsibility of the instrument/equipment manufacturer and should be carried out to approved written procedures using calibration test equipment that is traceable back to agreed-upon national standards. The test equipment must have precision, accuracy, and repeatability that are higher than that of the instrument being calibrated.

The pharmaceutical manufacturer is not normally represented at supplier factory calibrations but for critical items should consider an option to inspect instrumentation and witness tests. Calibration certificates referencing the test procedure and test equipment should be sought, particularly for the instruments and regulating devices directly associated with quality-related critical parameter measurements and control.

Instrument factory inspection and calibration must define what is required to verify compliance with the instrument data sheet. It should cover:

Operational requirements, such as working ranges and switch points
Physical requirements, such as materials of construction
Control characteristics and/or control logic requirements
Process connection requirements
Requirements such as supply voltage, signal type/levels, mounting, type of housing, cabling standards, and labeling

The procedure would typically include an inspection checklist, calibration procedure, test equipment stipulations, and documentation requirements (e.g., inspection certificates, calibration certificates, hazardous area certification, EMC/RFI certification, material certificates).

Instruments should not be released for installation on site until they have been inspected and calibrated in accordance with the approved procedure.

Q. Site Acceptance Test

Once the computer system has been delivered to the pharmaceutical manufacturer's site and is installed and connected through field cabling and tubing to instrumentation (and possibly other systems) it is ready for site acceptance testing—this for both critical and noncritical parameters and functions. The in situ acceptance testing of the system under the SAT is a key element of engineering commissioning. For continuity, SAT test results should be analyzed and compared to the FAT results.

In addition to proving the system to a level required by GEP, the site acceptance responsibilities should also incorporate:

Component unpacking, inspection, and storage
Computer installation and power-up
Instrument installation
Instrument recalibration
Loop testing
As-built engineering drawings
Installation report
System operating and maintenance manuals
Hand over to the pharmaceutical manufacturer

At this stage of a new installation it is possible that as-built drawings of the installation are still in a marked-up state. Marked-up drawings record the actual installation and should be submitted to the pharmaceutical manufacturer for review and approval before drawings are amended. The decision as to when to revise and reissue installation drawings can vary and will depend on the number of revisions, extent of revisions, and so on. A formal procedure is required to mark up drawings and control their use until drawings are updated and reissued.

Calibration of the instrumentation will be performed over the complete instrument loop. During each loop calibration, all data must be documented on appropriate instrument and loop calibration sheets and submitted to the pharmaceutical manufacturer for review, approval, and record. Calibration test equipment must be traceable back to agreed-upon national standards and documented on each calibration result sheet.

The calibration status and need for recalibration of instrumentation and associated regulating devices (see also Sec. VIII) during the implementation phases should consider the duration of the factory testing/delivery/installation period, manufacturer recommended frequency of calibration, and robustness and sensitivity of each instrument. The correct calibration of the in-line instruments, particularly those on critical parameter duty, is vital in achieving meaningful operational testing. For intelligent instruments (e.g., instruments that provide self-diagnostics and on-line calibration checking) the computer needs to provide appropriate records.

The site acceptance testing also provides an opportunity to identify and correct any problems due to shipping, utility hookup, hardware assembly, and field installation. The extent of SAT required can be determined by the completeness of the FAT, and as such is a full or partial repeat of the acceptance test specification with connections to the field instrumentation and regulating devices. Where it is not considered necessary to conduct a full repeat of the FAT, the rationale for this decision should be recorded in the qualification report.

The level of site acceptance testing should be such as to demonstrate satisfactory operation of the system functions in conjunction with the manufacturing process equipment and may involve control loop tuning. Site acceptance testing in its basic form should include installation checks, power-up, diagnostic checks, and commissioning of process and safety-related operational I/O, controls, sequencing, interlocks, alarms, and reports.

On satisfactory completion of SAT the system can be considered as available for plant operational commissioning. The computer system SAT report should document a high level of confidence in the computer system (i.e., the computer integrated with the field instrumentation and controlled function) in readiness for in situ site qualification testing activities.

Supplier acceptance test records and reports for both FAT and SAT should be approved and kept in the validation file.

Although supplier engineering contracts are usually fulfilled on satisfactory completion of the SAT, the performance of a computer system over a spread of data-handling conditions in the real-time environment of a manufacturing process is difficult to fully test at any one time. Consequently, consideration should be given to extending contractual conditions related to system performance into the system operational period, where the broader system performance issues can be better evaluated and reported.

In addition to demonstrating the state of readiness of the system, it is recognized that supplier acceptance testing as described above enables engineering commissioning activities and elements of in situ qualification testing to be combined. The pharmaceutical manufacturer may elect to do this when there is sufficient confidence in the system and process operation. Acceptance testing can also be considered as part of the training program for production operatives.

VIII. SYSTEM QUALIFICATION

Qualification is the process of establishing appropriately documented verifications and tests that provide a high level of assurance that a computer system will operate in accordance with predefined specifications. The specific approach to be used for each level of qualification should be outlined in the project validation plan and needs to focus on the critical parameters, data, and functionality of the computer system. While there are no absolute lines to be drawn between qualification testing of a computer system, it is recognized that the qualifications listed below provide the necessary control and continuity throughout the validation life cycle and must be approved for the system to be released for use in the GMP environment.

Design qualification
Installation qualification
Operational qualification
Performance qualification

For DQ (also referred to as enhanced design review) this means review of documented activities throughout the supplier's design, development, and build phases and can include FAT. This is followed by verification and testing of the computer system in its operating environment, under IQ, OQ, and PQ (see Fig. 2).

In some instances elements of IQ and OQ may be executed in conjunction with, or as part of, SAT and the associated project inspection and commissioning activities (see Fig. 3). Alternatively, IQ and OQ will commence after SAT and engineering commissioning is complete.

It should be recognized that qualification activities need to be undertaken to detailed test procedures that provide comprehensive test records, with all documentation formally reviewed and approved by a designated level of management from the pharmaceutical manufacturer. With this in mind, suitably trained qualification test personnel will be required.

Whatever the approach, consideration should be given to avoiding duplication of effort, and where possible qualification verification and test procedures should use or reference system acceptance and engineering inspection and commissioning documentation.

A. Qualification Protocols

The qualification protocol serves as a test plan to verify and document that a specific qualification has been satisfactorily completed. The qualification protocol and acceptance criteria are based upon the respective life-cycle specifica-

tions. The pharmaceutical manufacturer should have a documented procedure for the preparation of each qualification protocol.

The qualification protocol must be written and approved prior to execution of the protocol. Results of the executed protocol must be recorded and a summary report prepared.

To provide the recognized level of documented evidence qualification protocols should describe:

Test objectives and prerequisites
Responsibilities and signatories
Test or verification method
Traceability to specified requirements
Test data collection and record
Deviation procedure
Test procedure
Test data sheets
Qualification review and report
Supplementary data sheets

The tests should be designed to verify the existence of current and approved life-cycle and support documentation, verify system parameters, and test the technical functionality and quality-related attributes of the system, including safety, usability, and maintainability.

In detailing the test method, it can be beneficial to clarify the category of tests to be undertaken; for example:

Positive tests: Those that prove a certain condition exists (e.g., conformity testing)
Negative tests: Those that prove something cannot happen (e.g., challenge/boundary tests)
Proof tests: Those that prove an event can only occur under specified conditions (e.g., shutdown tests)

Test techniques that are to be used can also be identified; for example:

Valid case testing: A testing technique using valid (normal or expected) input values or conditions to prove the system performs as intended.
Invalid cast testing: A testing technique using erroneous (invalid, abnormal, or unexpected) input values or conditions to verify that the system prevents nonspecified operations that may cause dangerous situations or adversely affect product quality.
Stress testing: Testing conducted to evaluate a system or component at or beyond the limits of its specified requirements.
Volume testing: Testing designed to challenge a system's ability to man-

age the maximum amount of data over a period of time. This type of testing also evaluates a system's ability to handle overload situations in an orderly fashion.

Boundary testing: A testing technique using input values at, just below, and just above the defined limits of an input domain; and with input values causing outputs to be at, just below, and just above, the defined limits of an output domain.

Worst-case testing: This encompasses upper and lower limits, and circumstances that pose the greatest chance of finding errors.

Performance testing: Functional testing conducted to evaluate the compliance of a system or component with specified performance requirements.

Interface testing: Testing conducted to evaluate whether or not systems or components pass data and control correctly to one another.

B. Qualification Test Procedures and Results

To undertake each qualification, detailed verification and test procedures must ensure that the computer system is in accordance with the documented requirements and is traceable to specific specifications. These procedures may be included in the respective qualification protocol, along with clearly defined test acceptance criteria.

The computer system URS and FDS, the subsequent software and hardware design specifications, and instrument data sheets are the reference documents for qualification protocol development. The basis and acceptance criteria for each test should be derived from the system parameters, data, and function requirements that have been specified. It is advantageous to commence development of the test procedures at the same time as the respective specifications—this to best ensure that requirements and tests correspond, are traceable, and can be better understood.

Testing is to be conducted by designated test personnel. Each test result must be recorded (normally handwritten and initialed) by the person who conducted the test and similarly verified by a second person designated to check that the procedure has been carried out and the results are complete. Test results must be formally evaluated against the predefined acceptance criteria and the conclusions (e.g., unconditional pass or fail) recorded complete with an explanatory comment by a designated validation team member (normally the second test person). In instances in which a conditional pass conclusion is justified, this must be formally reviewed and rigorous controls imposed on the pass conditions. Approval and sign-off of the completed test records is normally the responsibility of the quality department representative on the validation team.

Any additional test data must be identified and appended to the test results. As appropriate, design reviews and the development and acceptance testing undertaken and documented by the supplier may be utilized to support the qualification effort and to optimize the resources required to achieve validation.

During qualification testing there may be instances in which the acceptance criteria for a particular qualification verification or test is not met. This must be identified (usually as a deviation) and the corrective action recorded, complete with plans for any retesting that may be required. The implementation of any resulting corrective action must be formally documented and test reruns approved and allocated a new test run number.

Test records should be kept in the validation file and used in preparing each qualification summary report.

C. Qualification Summary Reports

Each qualification must be formally reported to ensure an approved and auditable transition to subsequent life-cycle phases. Qualification summary reports for the system must be prepared by the pharmaceutical manufacturer and should be kept in the validation file. Each qualification report should confirm the qualification test acceptance and review associated change control records. The report must present a documented record that clearly states the basis for concluding that the qualification is acceptable, particularly *if* there are any minor conditions or actions outstanding.

The report must review the test results, draw conclusions, and make recommendations for future action (as applicable). This may take the form of corrective actions in the event of deviations or 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 qualification protocol.

A qualification report should include as a minimum:

Report reference number
Protocol reference number
Signatories
Start/finish dates
Qualification team
System and components identification
Methodology
Qualification results review
Deviations status
Change record review
Qualification status statement
Reference documents

Satisfactory completion, review, and reporting of each qualification, including those associated with field instrumentation and regulating devices, will release the computer system for the subsequent life-cycle phase.

D. Design Qualification

Design qualification is a formal and systematic verification that the computer system requirements specification is met by succeeding system design specifications and their implementation throughout the development and build (including development testing) activities.

Design qualification is normally a series of reviews of the software and hardware activities and documentation undertaken at appropriate stages throughout the design and development phase. The reviews need to consider all life-cycle design and development documentation and establish that software design, development, and testing is being conducted to written and approved procedures under a software quality assurance plan to meet operational and regulatory expectations. This ongoing DQ needs to address interpretation of user requirements by the FDS, system design specifications, system development practices, software review(s), all levels of software and hardware testing, and system release; identifying and reporting on the adequacy of the design and development, and provision of support documentation. A structured approach by the supplier to provide assurance that the system will perform as intended and is adequately documented for the GMP application will allow the pharmaceutical manufacturer to streamline its involvement in this phase.

The documentation for system design and development activities complete with development test results is normally prepared by the supplier. At a minimum, copies of the document reviews and a listing of the application development records should be provided for appending to the pharmaceutical manufacturer's DQ report. The pharmaceutical manufacturer may request copies of the supplier's application development and test records for inclusion in the validation file or arrange for the supplier to maintain and store all system application development records.

The DQ may also embrace the technical, quality, and commercial review of the inquiry/tender package conducted and documented by the pharmaceutical manufacturer. This is beneficial not only in checking that the computer system requirements have been adequately defined and are complete, but also in providing formal approval before the inquiry/tender package is issued and significant resources have been committed to implementing and validating the system. Any problems identified with the requirement definition at this stage can be more effectively resolved and the likelihood of omissions reduced.

A documented review undertaken with the vendor(s) to compare their FDS with the user requirements is necessary to record correct interpretation and un-

derstanding by both the vendor(s) and the user, and to verify traceability of requirements between the specifications. A key objective in comparing the URS and FDS is to confirm that an auditable system of documentation has been established that can be easily maintained throughout the validation life cycle. This will ensure controlled transition, with fully documented records, into the design and development phase that is normally carried out at the supplier's premises. Another important task is to identify system functions that are directly related to GMP and ensure implementation requirements for these functions are examined and reported in the GMP risk assessment for this step of the validation life cycle. (See Fig. 3 and Sec. IV.)

The use of a predefined checklist based on the URS to review the vendor documentation will assist the exercise and record that the key issues have been addressed in each one of the documents. The review team can also use the checklist to ensure that requirements are not duplicated and causing ambiguity.

In addition to the URS and FDS, other documents that are candidates for a requirement review include:

Project validation plan
GMP risk assessment(s)
Supplier prequalification response
Supplier audit report
Project and quality plans
Software quality assurance plan
Commercial and purchasing specs.
Supplier contract

The contract with the supplier may also be reviewed to verify the document deliverables and responsibilities.

On satisfactory completion of the requirement review and issue of an agreed-upon FDS by the chosen supplier, the design activities can proceed. Throughout design, development, and system build, the supplier, under its project and quality plan, must allow for review of life-cycle activities and documentation in support of the pharmaceutical manufacturer's DQ.

From this point in the design and development it is normally the supplier's contracted responsibility to lead the review activities and to provide all documentation and information necessary to undertake each review. To best ensure that the requirements detailed during the definition phase are fully covered by system design and development, the key review sessions should have appropriate representation from the groups primarily involved with the system application and operation and should verify adherence to the supplier's project and quality plan. This involvement will afford the pharmaceutical manufacturer a better understanding of the documentation that details how the supplier is meet-

ing the functional design stipulations, and this in turn will assist the software review(s).

Considering the activities required to systematically develop and test software and hardware, it is not unusual to have a series of reviews throughout the development and testing of software modules and hardware components, culminating with system assembly and integration. Review of the preparation of the instrument application engineering documentation and drawings should also be carried out, especially in relation to critical parameters. This approach will ensure that any problems or misunderstandings are identified early and enable effective resolution before software development and system build recommences, and will also provide a set of review documents that can be referenced in the DQ report.

At the end of system development testing and build activities the supplier will demonstrate how the computer system meets each requirement as defined by the FDS. This is normally contractual acceptance testing in the form of FAT and the SAT, and is witnessed by the pharmaceutical manufacturer with the intention of formally documenting that the system meets its design requirements and is ready for on-site qualification testing. Depending on the application and the project approach the DQ may be completed before or after the engineering SAT. If the approach is to finalize and report DQ before the SAT, then the SAT will need to be satisfactorily completed as part of or prior to commencing IQ.

The DQ report will address the actions and findings of the design and development review(s) and an agreed-upon level of formal acceptance testing. Satisfactory completion and documentation of the system design and development will allow the DQ to record that individual elements of the computer system have been adequately designed, developed, tested, and documented to meet the predefined specifications.

A review of the GMP risk assessment regarding previously identified critical system parameters, data, and functionality should also be undertaken at this time and reported as a section in the DQ report (see Fig. 3 and Sec. IV).

Documents generated for consideration in the DQ include:

Requirements review documentation
System design specifications
Software design methods
Software review(s)
System flow diagrams
Test procedures and records
Software release/replication procedure
Instrument data sheets
System and installation drawings
Deviation status list

Requirements traceability matrix
Configuration management records
Change control records
User operating manual
System manager manual
FAT report
Instrument calibration certificates
SAT report

On completion of the DQ process the pharmaceutical manufacturer's qualification summary report must record the completion of the DQ and acceptance of the system at site for the in situ qualifications required by the validation life cycle.

Installation qualification should not commence until the DQ summary report has been approved.

E. Site Instrument Calibration

As life-cycle qualification activities move to the in situ operating environment a methodical approach for the site calibration of control and monitoring instrumentation is needed to provide suitable calibration and any associated records for the loop instrumentation and regulating devices on critical parameter duty.

In addition to inspection and calibration of instrumentation carried out as part of an SAT, the need for recalibration of critical instruments prior to IQ, OQ, and PQ should be reviewed and the decision documented in the respective qualification report. All site calibration activity should be conducted in accordance with quality standards and the respective engineering procedures. Any remedial work should be undertaken under document control, and where necessary, evaluated under change control.

A written procedure must be in place to ensure:

Identification and labeling of instruments critical to the process.
Calibration to traceable standards.
Calibration at a predefined frequency.
Auditable calibration records are maintained.
Out-of-tolerance results are formally investigated.
Review of the satisfactory completion of the calibration procedure.

Calibration of critical instruments and system components must be controlled by a calibration schedule in order for call-off dates to be determined. The calibration periodicity should be determined by the process owner, its quality representative, and the maintenance engineer, taking into account the manufac-

turer recommendations and the robustness and duty of the instrument. In general, critical duty instruments are initially calibrated on a biannual basis (at a minimum) until there is sufficient historical data to determine reliability. The calibration status of critical instruments must be available and verifiable at all times.

Instruments must be calibrated to the appropriate site instrument calibration procedure using calibration and test equipment traceable to accepted national or international standards. Calibration procedures should be produced for each unique "type" of instrument. An instrument calibration procedure should:

- Identify instruments to which the procedure applies and any instruments of the same type that are specifically excluded.
- Identify precautions to be taken when carrying out the calibration and the source of any hazard.
- Describe the type(s) of instrument covered by the procedure.
- List the documentation that should be available before calibration commences.
- Describe the test equipment required to carry out the calibration test, including its name, model number, asset number (as applicable), range and accuracy, and any other applicable information.
- Describe the conditions under which the calibration must take place and identify the services required.
- Describe the detailed procedure to be followed to check the calibration of the instrument over its certified operating range and process failure limits (to ensure that it is within the tolerances specified in the manufacturer instruction manual and aligns with the requirements specified in the respective instrument specification/data sheet).
- Describe in detail the procedure to be followed for recalibrating an instrument that is found to be out of calibration when tested.
- Provide the calibration test sheet(s), applicable to the instrument under test, that should be used to record all test data necessary to satisfy the specified calibration requirements.

The results of calibration tests must be properly documented in accordance with the requirements of the manufacturer and/or the applicable national or international standard for the instrument before it can be considered calibrated.

The calibration test sheets form the evidence necessary to demonstrate the accuracy of data gathered during product manufacture and as such are key inspection documents. Critical instruments must be provided with a calibration test sheet/certificate that details both the test results and their limits of uncertainty. Calibration test sheets must be checked and approved by an authorized person.

Deviations from approved calibration standards on critical instruments must be reported immediately and investigated to determine if this could have adversely affected earlier testing or product quality since the last calibration.

If an external calibration laboratory is used it is important to review the scope of its certification with regard to any instruments that may be excluded.

Calibration records are normally stored in a dedicated calibration file along with the calibration procedures and calibration schedule. The location of calibration records (e.g., the engineering maintenance filing system) should be recorded in the validation file.

F. Installation Qualification

Conditional on satisfactory on-site inspection, assembly, installation, SAT, critical instrument calibration, and design qualification, the computer system is available for the in situ qualification phases.

Installation qualification is documented verification that the computer system (including all required software) is installed satisfactorily and is compliant with appropriate engineering codes, manufacturer recommendations, and approved specifications, and that the instrumentation is calibrated and all services are available and of adequate quality.

The IQ may require powering up the system and conducting a level of safety, environmental, and operation checks, and can be performed in conjunction with plant/equipment start-up commissioning.

The IQ testing will require a number of test and verification procedures to be satisfactorily carried out and documented to ensure all components of the computer system are correctly installed and recorded, demonstrating that the computer system is in a state of readiness to proceed to OQ. To accomplish this the following verification/test procedures must be covered by IQ protocol:

Validation file
Security access (area and system user)
Environmental
System diagnostics
Hardware component
Instrument installation and calibration
Electrical power and circuit protection
Instrument air supply
Loop wiring/tubing and cabling
Hardware configuration
Software installation
Software configuration
Software backup and restoration
General system inspection

The order of testing should be considered to ensure any instance of retesting is minimized, (e.g., document records need to be verified before documents can be used in other verifications/tests, and access security should be satisfactorily tested before system access is required for other qualification activities).

The IQ will include examination of all applicable documentation information, and for the verification of computer system records documents may be categorized as follows:

Qualification documentation: Documentation that must be present and on file before executing the remaining sections of the IQ protocol

System documentation: Documentation that must be present and on file in order to adequately record the computer system

Support documentation: Documentation that provides background information about the computer system application, but that is not essential to the execution of the IQ protocol or required to adequately document the system

Documentation will typically comprise validation life-cycle documents and procedures, SOPs, training records, quality records and procedures, process and engineering data, drawings, manuals, and spares list(s), and includes copies of the software. These originate from both the pharmaceutical manufacturer and the supplier. The documents must be verified as approved and on file under a document control system. The documentation must be located or stored in a controlled environment.

For hardware components, documentation detailing the performance capability, compatibility, and assembly must also be available, along with manufacturer model and version numbers and the serial numbers where available. Preassembled hardware that is sealed does not have to be disassembled if this breaks the warranty. In such cases the details may be taken from the hardware specification/data sheet and the source recorded.

On issue of a satisfactory and approved IQ summary report the computer system can proceed to OQ.

G. Operational Qualification

Operational qualification is documented verification that the installed computer system operates within established limits and tolerances as specified in the FDS.

The computer system must be powered up and checked to ensure it is functioning correctly. This may involve observing and recording system status lamps and/or rerunning diagnostic checks.

It is advisable to recheck the environmental conditions in which the system operates to ensure these are still within the manufacturer's recommended tolerances. Typical parameters that should be checked include

Air quality: temperature, relative humidity, airborne contaminants
Ventilation filters and flow rates
Radio frequency and electromagnetic interference (EMI)

Any abnormal conditions should be documented or reported and corrected prior to OQ testing.

Operation qualification involves a high degree of dynamic testing of the computer system in conjunction with the controlled process. It normally uses an alternative medium to represent process conditions, and can be performed in conjunction with plant and equipment engineering commissioning. Operation qualification testing may include both normal and abnormal operating conditions.

The OQ testing will require a number of test procedures to be satisfactorily carried out and documented to ensure all functions of the computer system are operating correctly and that the computer system is in a state of readiness to proceed to PQ. To accomplish this the following verifications/test procedures that focus on critical parameters, data, and functions must be covered by the OQ protocol:

Operator interface and screen displays
Input/output signals (including interfaces)
Data storage, backup, and restore
Electronic records and signatures, archive and retrieval
System report printout
Trend displays
Alarms, events, and messages
Process and safety interlocks
Control and monitoring loop operation
Software process logic and sequence operation
SOPs
Power loss and recovery

The order of testing should be considered to ensure retesting is minimized. Operator interface and screen displays are best tested before the system is used for other tests. Input/outputs need to be satisfactorily tested before other tests that are dependent on proven I/O signals, and trend display testing may be needed to support loop testing. For interfaces to other computer systems the main consideration is which system controls the access, selection, transfer, and use of validated data.

In considering electronic records and electronic signatures (ERES) the pharmaceutical manufacturer must address the system quality-related critical data collection and processing functions that come under ERES regulations (see Secs. IV and V).

Interpretation and intentions for ERES must be detailed in the validation plan, identifying the procedures to be used to verify and test compliance. These procedures must address both procedural and technological controls so that qualification testing demonstrates compliance with the clauses of the regulations that are applicable to the specific system GMP application.

Policies, training, and internal audits that support ERES should be verified, along with change control and configuration management records. To meet ERES regulations process control computer systems are now being developed with in-built configuration audit trail and software version management capability integrated with the system access security to provide automated revision history, version-to-version comparison, and version rollback, with configuration and runtime version linkage to enhance system integrity. Where applicable this functionality must also be tested.

Qualification testing of electronic records will need to:

- Verify GMP electronic raw data in the system
- Verify GMP electronic records within scope
- Justify electronic records not within scope
- Verify use of hybrid records
- Verify ability to generate paper-copy of electronic records
- Verify controls for system ("closed" or "open")
- Verify electronic record-responsible persons
- Verify access and physical security
- Verify operational checks
- Verify secure and nonmodifiable audit trail (system to document change, who made the change, what was changed, reason for the change, entry date and time)
- Test data integrity (backup/restoration, archive/retrieval/retention, discern invalid record, electronic records cannot be deleted)
- Verify accuracy of generated hardcopy
- Verify management, record, periodic revision, renewal, and misuse detection controls for password authority to electronic records
- Verify (for "open" systems) the use of document encryption and appropriate digital signature standards to ensure record authenticity, integrity, and confidentiality

Qualification testing of electronic signatures will need to:

- Verify electronic signatures applied to GMP electronic records
- Justify electronic signatures not within scope
- Verify within-scope electronic signatures as communicated to regulatory authority
- Verify individual responsibility/accountability for electronic signature

Test identification code/password or biometric electronic signature/devices (as applicable)

Test immutable linking of electronic signatures to electronic records (including signatories' printed names, execution time and date, and meaning of signature; e.g., review, approval, responsibility, or authorship)

Verify management, record (unique signatures), periodic revision, renewal, and misuse detection controls for electronic signatures

Approved SOPs must be in place before OQ commences. This will ensure operating instructions are performed in the same way each time and enable defined manual operations to be verified. Any revisions to an operational SOP (and associated documents) found necessary during OQ must be implemented under change control, and all affected documentation revised and reissued ready for retesting and use during PQ.

Operation qualification generally represents the first opportunity for plant operatives to use the computerized system in an operational condition and can be used as part of production personnel's training program on the system, plant equipment, and manufacturing process.

On issue of a satisfactory and approved OQ summary report the computer system can proceed to PQ.

H. Performance Qualification

Performance qualification is documented verification that the computerized operation (comprising the controlled process and the computer system) consistently performs as intended in the URS throughout all anticipated operating ranges.

For computer systems that are an integral part of the operation of a manufacturing plant or process, the system PQ may be conducted in conjunction with process validation. The combined activities are generally led by the pharmaceutical manufacturer's quality assurance function and can be in the form of an extended process trial.

This life-cycle phase will normally involve all parts of the computerized operation, not just the computer system. It is therefore essential that other equipment such as operating plant, utilities, and services that are part of or related to the manufacturing process have also been qualified or commissioned to the appropriate level prior to commencing PQ.

Performance qualification involves performing a number of production runs (traditionally, at least three) that are considered to be representative batch sizes for the operation. These are to be conducted using pharmaceutical product and utilizing the computer system and services of production operatives as stipulated in the URS and plant SOPs.

Before PQ can commence both IQ and OQ must be complete, with any actions related to critical parameters, data, and functionality satisfactorily resolved and documented. The computer system should be powered up and checked to ensure it is functioning correctly. The environmental conditions in which the system operates should be checked. Any out-of-specification conditions should be corrected and observations recorded.

There may be a significant time lapse between the OQ and PQ phases, and as a result, consideration must be given to whether any control and monitoring instrumentation needs to be recalibrated. It is advisable to recalibrate critical instrumentation under the site calibration procedures and so guarantee correct calibration prior to commencing PQ.

Performance qualification testing for the computer system will include a subset of the tests performed during the IQ and OQ phases in order to demonstrate in conjunction with the plant equipment and operating procedures that the system can perform correctly and reliably to specification. Focus will be on documenting how the computer system performs in controlling, monitoring, and recording critical parameters, data, and functions, and how effective and reproducible the system is under varying process conditions and data loading.

As relevant, OQ test procedures can therefore be used for PQ testing. In particular, consideration should be given to tests directly related to data integrity and system repeatability with focus on critical parameters; for example:

System access security
Diagnostic checks
Operator interfaces
Software installation verification
Software backup and restoration
Control and monitoring loop operation
Alarm, event, and message handling
Safety and operational interlocks
Software logic functions and automatic process sequence operation
Standard operating procedures verification
Data records and reports
Power loss and recovery

The documentation gathered for the PQ review must provide evidence to ensure that as a minimum:

The computerized operation consistently fulfills the operational and functional requirements of the URS and produces quality pharmaceutical product to specification.

There is sufficient information available to enable the computer system (hardware and software) and associated instrumentation to be operated and maintained safely and effectively.

All instruments deemed critical for product quality and safety are calibrated according to approved site procedures.

Batch production records are correct and suitably signed off.

Operations and maintenance personnel are trained to use the computer system to operate the manufacturing process under an approved training program.

Operational SOPs related to the computer system are in place and in use.

Operational plans are in place and viable, and include data record archives, maintenance procedures, and contingency plans.

On issue of a satisfactory and approved PQ summary report, it is demonstrated that the computer system supports the computerized operation, and conditional on satisfactory process validation is available for use in the GMP operating environment.

I. Validation Report

On satisfactory completion of the computer system qualifications, with PQ conducted in conjunction with a successful process validation, a final report must be prepared by the pharmaceutical manufacturer's validation team. This is normally referred to as the validation report. The objective of the report is to give an overview of the results of the execution of the validation program for the computerized operation and to draw a conclusion as to the suitability of the computerized operation for pharmaceutical manufacturing. This may be unconditional use or there may be restrictions. In the latter case the proposed remedial action(s) must be approved and, as applicable, considered under change control. A schedule to complete any outstanding actions must be documented and progress formally reported.

The validation report is a comprehensive summary that documents how the project validation plan has been satisfied. With reference to the qualification summary reports, the validation report serves as the approval document for all life-cycle activities and is the mechanism for releasing the computerized operation for pharmaceutical manufacturing use. Recommendations may be made for any follow-up audit or additional testing.

The report may follow the same format as the validation plan to aid cross-reference and must review all the key validation life-cycle documents. Any deviations and associated corrective actions should be reviewed, and any concessions on the acceptability of qualification test results examined.

The report should also preview the validation file documentation, control procedures, and support programs that are vital to the ongoing validation program and must be used as the basis for maintaining the validation status of the computer system. At this time a review of the GMP risk assessment should be undertaken and included as a section in the validation report.

The validation report should not be approved and issued until all control procedures and support programs are in place (i.e., system incident log, performance monitoring, calibration, preventative maintenance, document control, configuration control, security, training, contingency planning, internal audit, periodic review, requalification/revalidation, decommissioning/retirement). It is vital that the validation status of the computerized operation is not compromised.

The validation report must record all conclusions regarding the execution of the project validation plan, and for the satisfactory operation of the computerized operation in its operating environment it should be clearly stated as approved or not approved.

The pharmaceutical manufacturer must also set a regular review (e.g., annually) for ongoing evaluation of the computerized operation validation status.

IX. ONGOING EVALUATION

The purpose of ongoing evaluation (also referred to as the operation and maintenance phase) is to ensure that the computerized operation maintains its validated status throughout its operational life and that GMP-specific records are readily available for a stipulated period after the system has been decommissioned or retired.

This phase of the computerized operation is usually the longest phase of the validation life-cycle, covering the operational period of the computer system in pharmaceutical manufacturing.

During this period, and as relevant, the validation file must be updated with current and approved validation documentation that continues to provide evidence of a controlled and satisfactory validation life cycle and that will enable inspection readiness.

A. Validation File

The pharmaceutical manufacturer is responsible for maintaining the validation file and must ensure the computer system supplier(s) documentation is also up to date. The validation file document set must be under document control at all times, and is normally located in the pharmaceutical manufacturer's quality system to ensure controlled and expedient access at all times.

The validation file should have a file reference name and number and contain a document schedule or index with individual document titles, reference numbers, and version numbers. The file may also include electronic copies of documents (e.g., floppy discs, CD-ROM). Consideration should be given to

structuring the computer system validation file to reflect the validation life-cycle activities and include an introduction to the site, plant, process(es), product(s), responsibilities, and authorities. Typical document sets for the validation file are illustrated in Figure 5.

Documents that cannot easily fit into the validation file or may be required on a day-to-day basis (e.g., supplier system manuals, calibration schedule, and records) may be filed elsewhere, and these should be identified on the document schedule stating where they are located and identifying who is responsible for them. All documentation provided by the supplier must be suitably marked to easily identify its location in the validation file. It is acceptable to have the system development records archived by the supplier. If the pharmaceutical manufacturer requires the supplier to store and maintain the documents there needs to be a formal agreement on the retention period.

B. Periodic Review

An important objective of ongoing evaluation is to uphold an auditable system of validation documentation and ensure a controlled, fully documented record of any activity that may affect the validation status of the computer system and the computerized operation it is part of.

Written procedures shall define how the system will be used and controlled, and periodic review of these procedures and the validation documentation status must be carried out. The periodic review procedure should define responsibilities and should include predetermined criteria for reporting that computer system validation is being satisfactorily maintained in alignment with the project validation plan. A GMP risk assessment should form part of each periodic review to reconfirm (or not) the findings of the previous risk analysis and provide information for any revalidation that is considered necessary.

The periodic reviews will be event-based or time-based exercises. Event-based reviews will normally be carried out if there is a controlled change made to the computerized operation that is outside the scope of the original validation and could impact on process or product quality attributes. This will normally be conducted in conjunction with the change control procedure (see Sec. IX.C), and should include a review of all relevant validation documentation to determine the extent of revalidation that may be required.

Periodic reviews may also be prompted by reported or suspected problems with GMP compliance. When a periodic review determines a deviation from approved conditions or practices this must be investigated and corrective action approved. If there is a need to redocument or retest the computer system, then the need for revalidation must be assessed and the resulting rationale documented.

Time-based reviews should be planned for at defined intervals to check adherence to procedures and the currency of validation records. The frequency

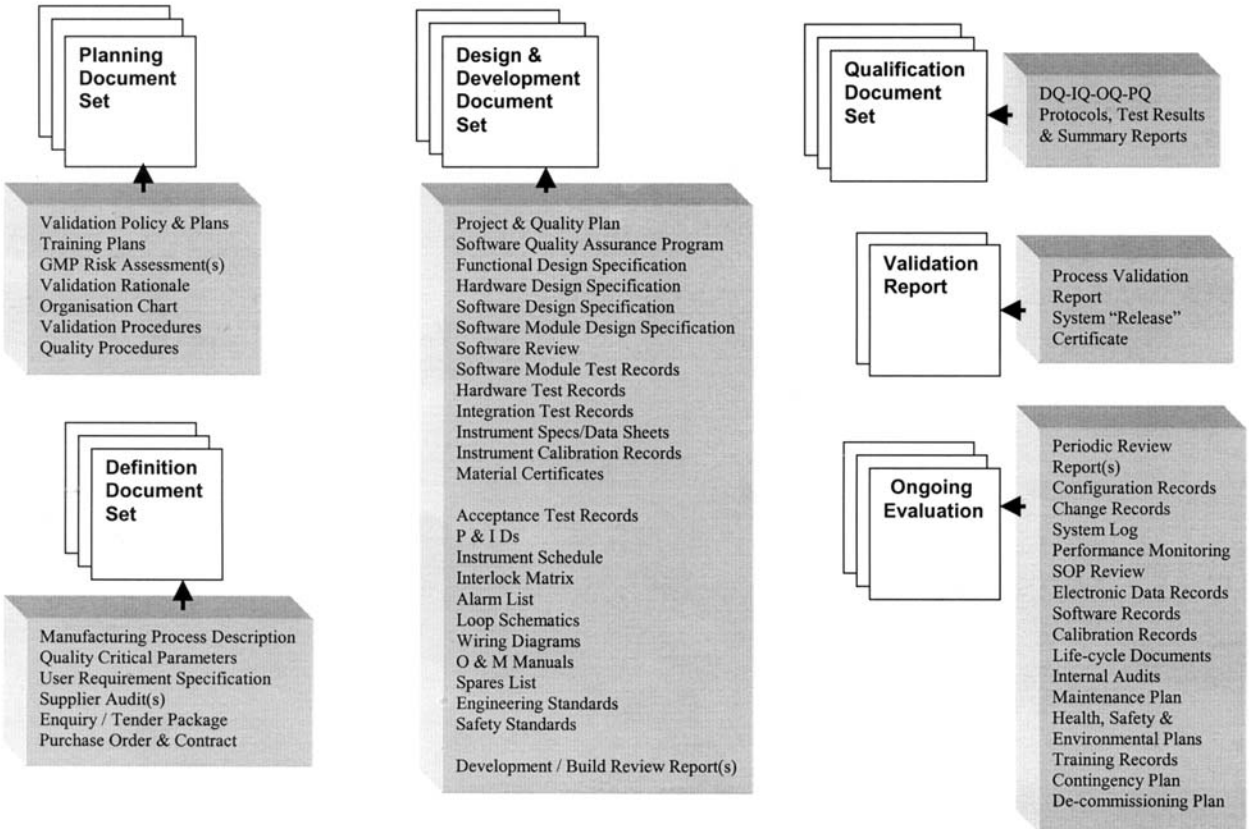


Figure 5 Validation file documentation.

of reviews can vary, depending on the application, and at a minimum are generally undertaken annually. Such reviews can be supplemented by internal audits to spot-check correct use of procedures and control of validation support documentation.

Consideration should be given to periodic revalidation to ensure the computerized operation remains capable of achieving the intended results. The extent of revalidation will depend upon the nature of the changes and how they affect the different aspects of the previously validated computerized operation. Unless circumstances demand, revalidation does not necessarily mean a full repeat of the validation life cycle. As appropriate, partial requalification may be acceptable. For instances in which new qualification testing is undertaken it is advisable to retain the original qualification summary reports in the validation file or quality system archives, marked "superseded" with cross-reference to the new documents.

Periodic evaluation should take into account all relevant sources of information and data that demonstrate the suitability of the computer system performance, including but not necessarily limited to:

Software/hardware changes
Trend analysis
Error and discrepancy reporting
Incident logs
Rework/reprocessing
Process failures
Product failures
Customer complaints

In addition, ongoing evaluation should address the following through the periodic review procedure:

Auditable validation life-cycle documents and software
Procedures/records
- Change control
- Configuration control
- Document control
- On-site work procedures
- System security (closed and open systems)
- Data backup integrity
- Data records archive/retention/retrieval (electronic records and paper copy)
- Contingency planning
- Revalidation
- Decommissioning/retirement

Training plans and records
Operational/maintenance plans and records
  Process SOPs
  System incident log and problem reporting
  Performance monitoring
  Calibration
  Preventative maintenance
Health, safety, and environmental plans and records
Operational environment issues
Periodic review summary report

For electronic records the following should be addressed:

Alarm logging, events, errors, real-time and historical trend data where used for regulatory purposes.
Electronic data associated with configuration parameters.
Electronic records that are printed to paper are linked to electronic form.
Archived electronic records stored on maintainable media and in a format that can be read at a later date.
Version control of software source and application code.

For the life-cycle validation documents and any associated support documents that make up the validation file the periodic review must verify that these are approved and auditable, and maintain traceability between related documents.

Operational and maintenance plans should be prepared for the computer system and its associated measurement and control instrumentation. Operational plan review will focus on system reliability, performance, diagnostic records, instrument and system I/O calibration, and the provision of critical data to support the batch record. Procedures for controlling the system (e.g., system management, security, and process operations) should be reviewed to verify that they are current, in place, and being followed. For each procedure required for the system there should be documented evidence that the relevant operatives have been trained in its use. All procedures must be written and approved according to the site procedures for writing and approving SOPs.

The maintenance plan will normally form part of the preventative maintenance system for the site and must be used to track all maintenance activities on the computer system and associated measurement and control instrumentation. For computer systems the supplier may be contracted for different levels of ongoing maintenance support, and it is acceptable to use the supplier procedures for maintenance of the specialist areas of the system. A supplier maintenance contract needs to define the scope of maintenance (e.g., the items to be maintained, type of activities, period of the contract, access requirements,

procedures to be followed in conducting, recording, and reporting maintenance, trained resource, and response times). Maintenance activities will cover three main areas.

Normal operation—The computer system is maintained in accordance with the planned preventative maintenance schedule. Typical activities include recalibrating field instrumentation and computer I/O cards in accordance with site calibration procedures, running system diagnostics, checking operator logs for any abnormalities, and planning service visits by the system supplier.

Abnormal operation—A failure occurs with the computer system or with the measurement and control instrumentation and an emergency repair is carried out either by site engineering or by the system supplier under the terms of the support agreement. In emergencies, immediate action may be authorized by the production department in conjunction with quality assurance, the problem, the action taken, and the updating of all affected documentation recorded retrospectively for change control assessment.

Modifications and changes—Planned modifications and changes during the life of the computer system and measurement and control instrumentation should be carried out in accordance with the site change control procedure.

C. Change Evaluation

For any changes an impact assessment must be performed as defined in the change control procedure. This assessment will consider:

Scope and rationale for the change
Impact on product quality
Impact on system validation status
Requalification/revalidation actions
Documentation to be generated
Authorization level required

The assessment will then decide on the disposition of the change (accept, amend and resubmit, or reject). All approved changes should then be passed to a designated "implementation group" that will be responsible for ensuring that the change control procedure is followed.

The implementation group must align its activities to the validation lifecycle documentation to ensure the design and application engineering necessary to implement the change is conducted in a structured manner and to ensure any retesting of the system is conducted at a level necessary to embrace all change issues.

For changes to the computer system, appropriate representation from both the pharmaceutical manufacturer and the computer system supplier should be considered. The pharmaceutical manufacturer remains responsible for ensuring that the validation status of the system is maintained.

As the first step in implementing any controlled change on a computer system, the scope of work should be determined and documented. This will provide a comprehensive list of all controlled items, as well as any uncontrolled items that require modification as part of the change. This should include:

Definition documentation
Design/development documentation
Qualification documentation
Ongoing evaluation documentation
System software
System hardware
Measurement and control instruments
System security and data integrity

In most instances and due to the system validation life cycle, a modification to a high-level document will invariably affect lower-level documents. These lower-level documents are called "dependant documents," and it is important to identify and update all affected documents.

When all the directly (and indirectly) affected items that require modification have been determined the components and functions of the system directly and indirectly affected by the change can be identified. At this point a review of the system GMP risk assessment(s) should be undertaken and the potential for revalidation addressed. Reference to the life-cycle model will identify the specification for each item and point to the qualification test procedure(s) that need to be considered.

The respective qualification or testing document should be examined to assess whether existing test procedures are suitable or whether enhanced or additional test actions and acceptance criteria need to be prepared. The rationale and required level of qualification testing for any revalidation should be documented in the change records and the validation plan suitably updated.

Following the requirement for identification of indirectly affected items it is logical to ensure that these are also tested to an appropriate level. In most instances the indirectly affected areas can be tested using a technique called "regression testing." Regression testing is where the results of previous tests are compared with the results of postmodification tests. If the results are exactly the same then the indirectly affected item can be considered as operating correctly.

All revised documentation must be checked and approved by designated personnel and placed in the validation file. All superseded documentation must be marked as such and dealt with in accordance with site quality procedures.

D. Decommissioning

The ongoing evaluation process should also consider system decommissioning in readiness for eventual system retirement. Initially a plan should be prepared to identify GMP requirements and the validation considerations for system retirement. Then, in readiness for the actual decommissioning, a detailed procedure is required specific to the current operation of the computer system and its GMP-related quality-critical data. Any retesting required in support of decommissioning is to be included in this procedure.

The decommissioning procedure must address both operational and safety aspects of the computer system application and establish integrity and accuracy of system data until use of the system and/or process is terminated. For quality-related critical instrumentation, proof of calibration prior to disconnection is needed.

The procedure should include review of all the collective information in the validation file to confirm the validated status of the system and ensure data records that are to be retained in support of released product are available. The requirements necessary to conduct and report the archiving of GMP records need to be defined, and should identify all life-cycle documents, electronic raw data, electronic records (including associated audit trail information), and system application/operating software that are to be archived.

It must be possible to reproduce the archived data in human-readable form throughout the retention period. Where applicable, the method of data transfer to any other system must also be formally documented and controlled.

Computer system decommissioning can also encompass disconnection, disassembly, and storage (or mothballing) for future use. Accurate specification, design, development, qualification testing, and operational documentation is essential to enable controlled redeployment of the system in a GMP environment.

E. Periodic Review Report

A periodic review meeting should document the review process, documents reviewed, comments from attendees, and the collectively agreed-upon course of action. The periodic review summary report should record the findings of the review meeting and include an action schedule itemizing any documentation that requires updating and those responsible for completing the work. The progress of updates should be monitored through the documentation management system against agreed-upon completion dates.

Following a successful periodic review, acceptance of the evaluation should be clearly stated in the periodic review report and approved by the system owner and signed by designated members of the validation team.

The periodic review report(s) should be retained in the validation file as a record of the computer system validation of the validation status and the validation plan should be updated with a date for the next review.

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