
PDA
An International Association For
Pharmaceutical Science And Technology

Validation of Computer-Related Systems

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1.0 Introduction

In recent years there has been a significant increase in the use of computer-related systems in the pharmaceutical industry.It is clear that these systems must satisfy GMP requirements,but legitimate questions have been raised concerning the scope and methods which should be employed in validating computer-related systems. While there is little question that the end user is ultimately responsible for assuring that systems used in GMP applications are in compliance with the regulations,most end users rely heavily on vendor-supplied information and test data to support their system validation.What requires further clarification is the extent of testing and the type of documentation required to validate a computer-related system in an acceptable manner and how to delineate vendor and user responsibilities in vendor-supplied systems.

The PDA Committee on Validation of Computer-Related Systems was formed to address some of the issues associated with validating computer-related systems,including those cases where all,or part,of the computer-related system is supplied by an outside vendor.This report describes a method emphasizing computer-related system requirements,computerized system specification,computerized system qualification, and ongoing evaluation.While some of the specific procedures are appropriate only for the case where the vendor is an outside contractor,the general method presented also applies to the case where the vendor is an internal development group.

There is no intent to present this as the only acceptable method.To the contrary,validation of computer-related systems is often complex,and any number of alternate approaches may be used.The scope of any validation effort depends upon a number of factors, including the size and complexity of the system and whether the functions are critical or noncritical in nature.

2.0 Scope of Document

This report identifies factors to be considered and steps to be taken in selecting,installing,and validating computer-related systems used in pharmaceutical GMP functions.It does not apply specifically to medical device or GLP applications,but the validation principles in

those applications would be similar.The purpose is to provide information about validation concepts and to describe some of the practical documentation that may be used to demonstrate proper performance of computer-related systems.The examples should be considered instructional rather than all-inclusive.When appropriate,factors in addition to those contained in this report should be considered.The method described in this report is consistent with the PhRMA(formerly,the PMA)Computer System Validation Committee's Life Cycle which focuses primarily on the definition,development,and qualification of computer-related systems. Figure I gives a version of the PhRMA Life Cycle which is modified to include the term,“Computer-Related System.”

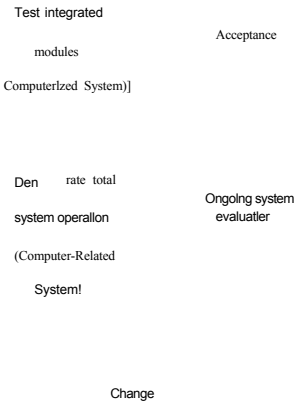
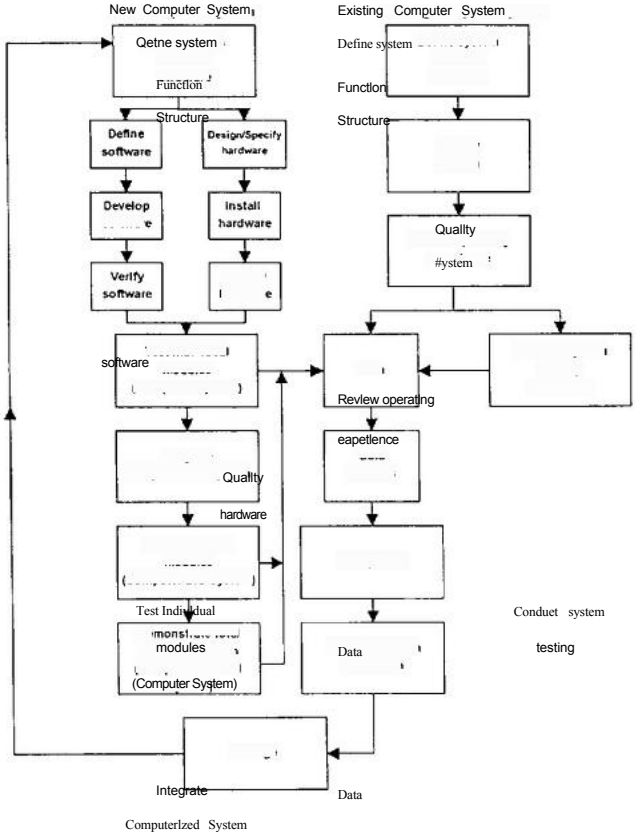


Figure 1—The lfe cycle approach to computer-related system vall- dation

3.0 Validation Concepts

3.1 Computer-Related System Definition

Figure 2 provides a graphical view of various system concepts.The computerized system is composed of the computer system and the controlled function.The computer system is composed of computer hardware,including all of its peripherals,and software controlling the operation of the computer.The controlled function may be composed of equipment to be controlled and operating procedures that define the function of such equipment,or it may be an operation which does not require equipment other than the hardware in the computer system.The equipment considered in this report may be



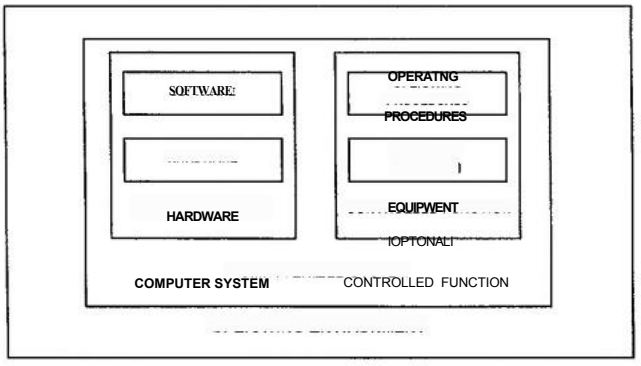


Figure 2—Computer-related system

manufacturing or laboratory equipment used in a GMP function.

The computerized system functions in an operating environment which includes information input from operators or from other sources,input of material to be processed,the physical environment,plant support utili- ties,and any other factor which might affect the state-of- control of the computerized system.A computer-related system is a computerized system performing its intended function in its operating environment.

A computer-related system executes a process.As used in this document,the term“process”is not restricted to a manufacturing process.It may be a laboratory process,a document control process,a data management process,or any other process requiring validation.In many cases a computer-related system will be applied to automate an existing manual or semi-automated process such as inventory control or document control.A computer-related system cannot be validated unless the process it is executing can be validated.

3.2 Process Validation

The FDA Guideline on General Principles ofProcess

Validation defines validation as“Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.”According to current interpretation,validation is the entire procedure of gathering documented evidence that a process or a system performs its intended function reliably and consistently.To avoid confusion,the term"validation" should not be used for any specific type of testing or protocol.It is recognized,however,that IEEE/ANSI and ISO standards define “software validation”as the process of evaluating software to assure compliance with specified requirements,which is an appropriate definition for that purpose.

3.3 Computer-Related System Validation

Following the definition of process validation as closely as possible,computer-related system validation can be defined as “Establishing documented evidence which provides a high degree of assurance that a specific

computer-related system will consistently operate in accordance with pre-determined specifications."It is important to introduce the concept of computer-related system validation,in addition to the FDA definition of process validation,because some systems which must be validated are not directly involved in the processing of a product.

4.0 Validation Procedures

This document describes one approach to validating computer-related systems that emphasizes the importance of defining computer-related system requirements and developing a comprehensive computerized system specification based on the computer-related system requirements.Figure 3 illustrates eight logical steps that are included in most validation programs for computer-related systems.These eight steps begin with preparing a written validation plan and defining requirements for the system.It is assumed that the user firm has appropriate policies and SOPs for validation activities.If they do not,it is important that such documents be prepared.

The steps of Figure 3 are not necessarily executed in the order indicated.Rather,the eight steps are usually executed as an iterative process where various functions may be carried out concurrently;and,if necessary,steps may be repeated.For example,the validation project plan may be developed after or concurrently with the computer-related system requirements rather than before as is indicated by Figure 3.The selection of equipment and software and the establishment of written specifications involve a series of steps which are extremely important in any validation program,particularly where vendor support is required in the testing and in the documentation of a system.

Some of the steps of this method will not be required in some validation projects.Many firms have selected certain software and hardware products which they use whenever it is possible to do so.In those cases,many aspects of defining the system and selecting the vendors described in this report may not be required.Figure 3 addresses the more complex example of a larger system where the computer system and the controlled function equipment are developed separately and may be obtained from different vendors.In the case of a packaged system performing a unit operation,the computerized system typically is purchased from one vendor and the design is integrated from the beginning.When standard systems are to be used,many of the steps relating to the design and construction of the systems will have been taken in the past.Obtaining documented evidence that a system was designed and constructed according to appropriate quality standards is an important part of validating a computer-related system,even when those activities occurred in the past.

While the procedures described in this report are intended primarily for new systems,the principles also apply to existing systems.For systems that have been in use for some time,a compilation and review of documentation and historical data supplemented by a series of

functional tests may be adequate to show that the system is in a state of control.Evidence that the software is structurally sound may be provided by a formal evaluation of the vendors'software development and testing procedures and,in certain circumstances,by an analysis of historical system-related data.

During any project it should be expected that changes and modifications will be made based on test data and experiences gained during the development,integration, and qualification steps.The validation method described in this report accommodates changes at all steps, but it requires that such changes be made in accordance with written procedures and that they be documented appropriately.The arrows pointing upward in Figure 3 indicate that information obtained at that step may require changes in designs and documents that were created in previous steps.

4.1 Plan Validation Activities

4.1.1 Validation Policies:Policies define general principles and practices that are required by a firm.Each firm should have written and approved validation policies communicating management's expectations for execution of validation projects.Within any given firm there may be multiple sites,each having different validation requirements and,perhaps,different validation practices.While conforming to the overall corporate policies,site policies generally provide more detail on the requirements of a specific site.Policies are intended to establish responsibilities and expectations.

Policies do not normally specify specific testing requirements.

4.1.2 Validation SOPs: Standard Operating Procedures (SOPs)provide detailed instructions for executing specific tasks or assignments.The designated quality unit in a facility should prepare,or have prepared for approval,appropriate written validation SOPs that establish clearly which operations need to be documented, what information the documents should contain,how critical information should be verified,who is responsible for generating the documentation,and what approvals are required for each document.There should be specific SOPs for the validation of computer-related systems.Protocols should be developed,test data reviewed, and summary reports written in accordance with written procedures that assure validation objectives are met.

The firm's validation SOPs should specify whether separate or integrated protocols and reports are to be prepared for installation qualification,operational qualification,and performance qualification.They should also specify the personnel responsible for reviewing and approving protocols,test data,and reports.Responsible personnel are usually specified by job title.As is the case in all GMP documents,the significance of each signature in reflecting the nature and extent of review, evaluation,and approval should be in writing.

4.1.3 Validation Project Plan:Plans provide orderly arrangements for accomplishing specific objectives.The purpose of a validation project plan is to identify the

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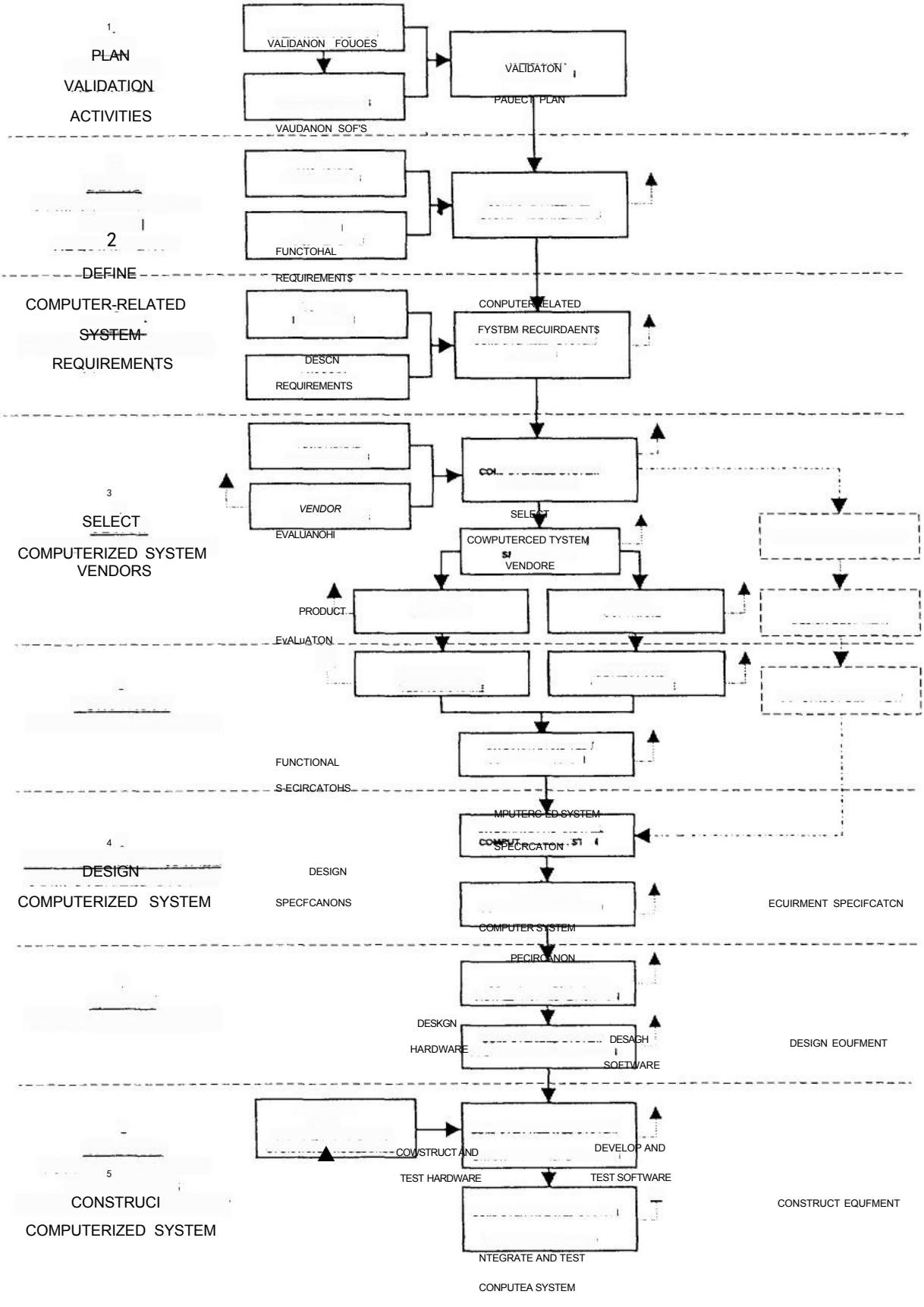
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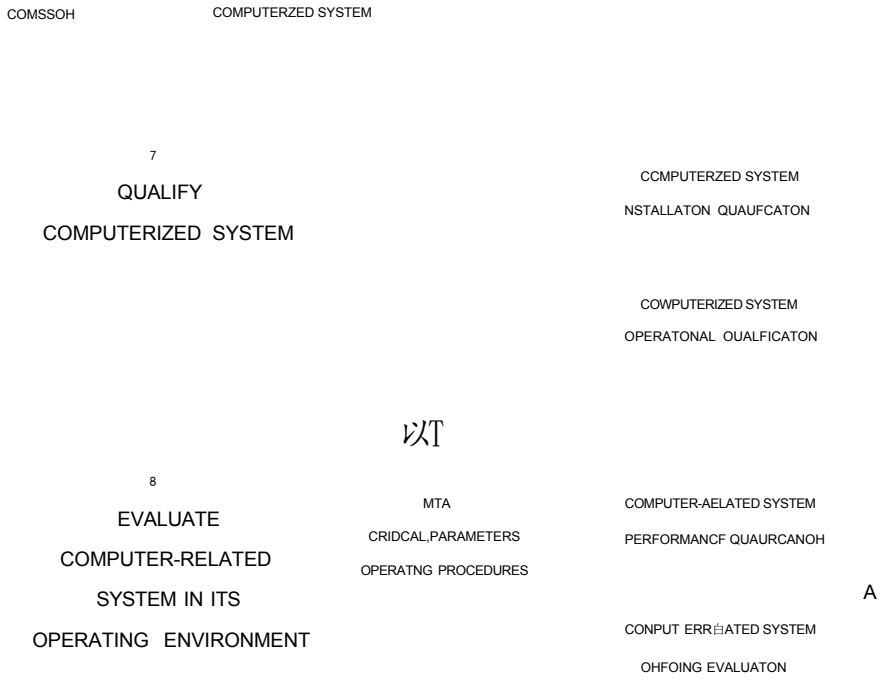

Figure 3—Steps in validating computer-related systems

systems to be included and the procedures to be followed in a specific validation project.The procedures described in a validation project plan should be consistent with established policies and should reference the appropriate validation SOPs.A validation project plan may be written for a single system or for an entire facility.While it is clear that the firm's quality unit has primary responsibility for all specifications and procedures affecting the identity,strength,quality,and purity of the drug products produced in a facility,an important

purpose of a validation project plan is to establish specific responsibilities and expectations for each validation task.

4.2 Define Computer-Related System Requirements

Defining the requirements for a computer-related system is one of the most important steps in assuring that the system meets the user's expectations.The computer-related system requirements document is the foundation for the computerized system specifcation and all subsequent design documents.A successful validation project depends upon a proper definition of what a system is supposed to do and a clear understanding of the requirements at a level which is independent of specific hardware or software unless the use of specific hardware or software is a requirement.

Figure 3 shows the relationship of several aspects of defining a computer-related system.Functional requirements define“what”the system must do to be acceptable for the application.Design requirements define the structure of the system and other physical attributes. There should be a written description of the process that the computer-related system is intended to execute. That document,or collection of documents,is often called the process description.Information such as the sequence of operations is often included in the process description.While the scope of this report does not include validation of the process,a process description is important in defining the requirements of a computer-related system.

Computer-related system requirements should be defined by a team which includes the users and all other disciplines involved in the design,implementation,validation,operation,and maintenance of the system. Through an iterative process requiring close cooperation and effective communication among all members of the team,including potential vendors,the preliminary concept of required features is refined to identify those features which must be satisfied and those which are desirable.The desired features should be prioritized as to their relative importance.Features which are necessary in order to validate a system should always be considered requirements,not desires.Appendix 1 gives an outline of information which should be considered for inclusion in a computer-related system requirements document.

Not all projects require a formal request for proposal, but when one is prepared for a project it should include the information contained in the computer-related system requirements document.Since prospective vendors prepare their responses on the information contained in the request for proposal,it is important that the information be complete and accurate,as it forms the foundation upon which the quality of the system will be built.

4.3 Select Computerized System Vendors

As used in this report,the term “vendor”applies to an internal development group as well as an outside company.Selection of the vendor or vendors of components

of a computerized system should be based on the computer-related system requirements.Whether the vendor is an outside company or an internal department, the vendor's ability to provide a system which can be validated should be a primary consideration.Selection of the components of a computerized system involves evaluation of the vendors as well as evaluation of the proposed hardware and software.

4.3.1 Vendor Evaluation: A suitable vendor will be technically competent and commercially qualified to supply and support the proposed system.Knowledge of validation requirements and experience in providing systems for GMP applications are important selection criteria.If application-specific software is being developed,the vendor's software quality system should be a major factor in evaluating the capability of the vendor to provide an acceptable system.Qualifications of selected vendors should be verified through on-site evaluations focusing on the vendor's quality system.One purpose of a vendor evaluation is to determine the extent of testing the user will have to perform in order to provide a high degree of assurance that the system will operate in the intended manner.Specific areas to be evaluated include the adequacy of development plans,test plans,software audit programs,and internal training of management, engineering,and software development personnel.Appendix 2 gives an outline of factors which may be included in vendor evaluation.It is important to verify the use as well as the existence of quality standards.

4.3.2 Product Evaluation: The relative importance of selection criteria for software depends upon the type of software being evaluated.For commercial,off-the-shelf programs,such as an operating system or a commercial, off-the-shelf confgurable program,the history of satisfac- tory use is often of major importance.A retrospective analysis of software problem reports,the procedures used by the vendor to correct them,the number and type of applications using the program,and the length of time the version to be purchased has been in use can provide convincing evidence that a program is structurally sound. If software is being modified or developed specifically for the application,primary emphasis should be placed on evaluating the vendor's Software Quality Assurance (SQA)system.

Hardware evaluation may be as complex as software evaluation.Similar engineering and quality rules for development and maintenance of hardware need to be demonstrated by the vendor for both standard and custom hardware elements.Like software,standard hardware components can be evaluated based on similar criteria for retrospective analysis.Some key evaluation points include usage history,durability,reliability,and accuracy while operating in the defined conditions of the customer's environment.

Many automation solutions contain a hybrid combination of software and hardware called "firmware,"which is a term used to describe software instructions recorded in special hardware read-only memory devices such as Programmable Read-Only Memory (PROM).Software

destined for firmware should be developed,tested.and maintained in the same manner as other software intended for similar use.Therefore,it should be evaluated in the same manner as other software.Manufacturing controls for replication of firmware,product testing. release,labeling.and version clarification should also be evaluated for compliance with written manufacturing standards and practices.

4.4 Design Computerized System

The computerized system specification is an essential document in the validation of a computer-related system.It is the document,or collection of documents, which describes clearly and completely how the computerized system will operate and how it satisfies the computer-related system requirements.It is the basis of the qualification protocols for the computerized system. The computerized system specification should identify all measurable or determinable parameters which may affect performance and include the acceptable values or characteristics of each critical parameter.A critical parameter is one which will affect the state-of-control of the system if it deviates from an acceptable range of values.

Computerized system specifications apply to both the computer system and the controlled function and should contain all of the information required to describe how the system will operate in all of its normal operating modes and how it will respond to abnormal conditions. Computerized system specifications cannot be developed until the vendors and the specific hardware and software to be used have been selected.The development of the computerized system specification should be a joint responsibility of the vendors and the user.It is important that the computerized system specification contain detailed information about the interfaces between the computerized system and its operating environment.

The computerized system specification should be a written and approved document or collection of documents which answer all important questions about the installation and operation of the system.It may refer to other documents such as the process description,the computer-related system requirements,construction drawings,equipment manuals,or SOPs for more detailed information.It is anticipated that changes to the computerized system specification will be required based on information gained during the development,installation,and qualification of the system.Once the computerized system specification has been approved,all changes should be made according to change control SOPs which assure that all related documents such as program listings,operator manuals,and installation drawings are modified to reflect the changes.Appendix 3 gives an outline of information which should be considered for inclusion in a computerized system specification document.It should not be surprising that the information in Appendix 3 is very similar to that in Appendix 1.because an important step in validating a computer-related

system is verification that the computerized system specification addresses all of the requirements in the computer-related system requirements.

In more complex systems,it may be desirable to have a separate computer system specification and even a separate software specification document if a significant amount of code is being developed for the project.In cases where the controlled function does not include equipment,it may not be necessary to have separate documents for the computerized system specification and the computer system specification.

Figure 3 shows an example where the computer system and the controlled function equipment are developed separately and may be obtained from separate vendors and integrated at the user's site.The dotted blocks in the right portion of Sections 4 and 5 of Figure 3 indicate that activities similar to those described here for the computer system must be carried out for the controlled function equipment.If the computerized system is a packaged system purchased from a single vendor,it will usually be integrated at the vendor's site.

4.5 Construct Computerized System

The example in Figure 3 addresses a system where a significant amount of software is developed for the application,and the computer system and the controlled function equipment may be purchased from different vendors.From a validation perspective,the area of greatest concern in this type of system is the development and testing of the software.

4.5.1 Types of Software: In the following discussion, three categories of software are described;system software,configurable software,and application-specific software.These classifications are not considered to be rigid,but they allow important distinctions to be made about vendor-supplied software and software testing.

System software provides basic operating instructions for the computer and controls operations such as resource allocation,scheduling,input-output functions, and data management.An example of system software is an operating system such as MS-DOS or UNIX.Generally,system software is independent of the specific application.

Configurable software allows the user to define a number of conditions such as operating parameters, reporting parameters,and alarm conditions.The user does not change the configurable program code itself but can change the parameters to satisfy the requirements of the application.Examples of configurable software are Lotus 1-2-3 and most Distributed Control Systems (DCS),Supervisory Control and Data Acquisition (SCADA)systems,and Programmable Logic Controller (PLC)programs.If the program code of configurable software is altered for the application,the code is considered to be application-specific software.

Application-specific software is code which is written or modified for the specific application.When configu- rable software is used to implement application-specific software,the parameters which specify the operations of

the configurable software should be divided into two categories;those parameters which are accessible to the operator at run time,and those which are not.The parameters which are modifiable by the operator should be considered data and recorded as such.The parameters which are not modifiable at run time should be documented and secured as part of the application program.Any changes to the parameters comprising the application program must be done according to approved change control procedures.

4.5.2 Software Testing: The purpose of software testing is to provide a high degree of assurance that the system using the software operates in accordance with the system specifications.Testing of software to be used in a computer-related system should include both structural verification and functional testing.Structural verification of software includes detailed examination of the functional logic of code to verify that it conforms to software requirements and specifications.It also includes inspection of the program for adherence to software development standards and procedures.Structural verification may include specific activities such as branch testing,path testing,and statement testing. Structural verification of software can be done effectively during software development.This is particularly true of configurable software.

Functional testing of software is a thorough and systematic comparison of observed output values of a program with expected output values for a specified range of input values and other specified parameters. Functional testing may be performed using simulated inputs to the software or by testing the computer system or the computerized system.

Source code must be available to perform structural verification.It is also important to have other program documentation such as logic diagrams,description of modules,definition of all variables,and specifications of all inputs and outputs.If the vendor can provide sufficient documented evidence that configurable software is structurally sound,it may not be necessary for the user to perform structural verification to assure proper operation.The user should perform structural verification of application-specific software.

Functional testing of software does not require source code,but it does require a comprehensive computerized system specification or a computer system specification describing all functions of the system in sufficient detail to define the tests required to assure that the system will operate in the intended manner.Complete and accurate descriptions of all functional routines such as calculation algorithms and control strategies should be available to the user,and while the availability of source code is not required for functional testing,it may be helpful.As in the case of structural verification,it is important to have program documentation such as logic diagrams,descriptions of modules,definitions of all variables,and specifications of all inputs and outputs.

4.5.3 Software Quality Assurance: Software Quality Assurance(SQA)is a defined and systematic set of

activities necessary to provide adequate confidence that a software item or product conforms to predefined specifications.Defined processes,assigned responsibilities,established practices,planned audits,structured reviews,and management controls,collectively,promote an environment where product quality is managed throughout development,testing,and maintenance phases.Established practices for software development include the use of written standards,procedures,and guidelines.

Auditing a software vendor is a valuable means to obtain information on product development practices, maintenance controls,and the quality methods employed.The limitation of auditing is that demonstrated conformity to a formal SQA system does not guarantee product quality.It provides evidence that a quality system is in place to achieve and manage product quality.A more extensive evaluation of a vendor's methods,to supplement or replace a normal audit,may have additional benefits to users acquiring software products.Such an evaluation can be focused to derive maximum benefits from the vendor's activities that support quality and validation requirements.

Documented evidence that a vendor's activities conform to a defined quality system provides the user with assurance that a software item has been developed, tested,and is maintained with quality objectives.In most situations,the procedures employed by a vendor to develop and test a software product are adequate for that vendor's business needs.Information obtained by the user about the vendor's methods should provide a clear understanding of what additional effort will be required in order to use a software product in a GMP application.

In the case of custom software applications and configured sofware products,the completed software entity does not exist at the start of the project.The software will have to be constructed and tested based on defined requirements.A structured SQA system is designed to evaluate a software product during various phases of development and testing,assuring that the completed deliverables will be in compliance with writ- ten specifications,standards,and practices,thereby increasing the chance for success in meeting both product and validation requirements.

4.6 Integrate and Install Computerized System

Proper integration,installation,and commissioning of a computerized system is essential to the successful qualification of the system.The procedures employed will depend upon many factors,including the type of system and the application.The procedures to be employed in any specific project should be specified in the validation project plan.

A packaged system including equipment will usually be integrated at the vendor's site,and many of the adjustments and operating parameters will be set there. The user may require a formal Factory Acceptance Test

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