

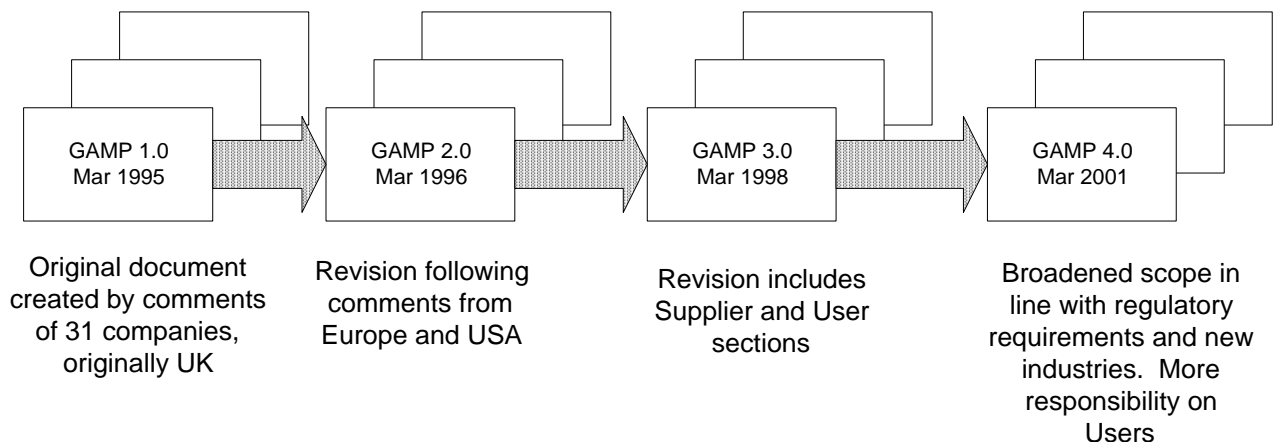
# Technical Document Review: Good Automated Manufacturing Practice (GAMP®) Guide for the Validation of Automated System

## Introduction

This document aims to review the Good Automated Manufacturing Practice Guide for the Validation of Automated System (GAMP® 4), December 2001, published by the ISPE. To learn more about GAMP® or to place an order, visit [www.ispe.org](http://www.ispe.org) The content of this summary hopes to identify the top level requirements of the steps undertaken to validate an automated manufacturing process, this includes environmental monitoring systems, autoclaves, filling lines, and any other process governed by electronic control rather than a manual process.

In the late eighties and early nineties the validation of automated system in pharmaceutical manufacturing assumed a much greater importance than had previously been the case. Although regulatory guidelines concerning the use of such automated systems had been available for some time, the systems had been subject to less regulatory scrutiny than other areas of production and were deemed to be less mature than more conventional areas.

An industry group was set up to promote the understanding of the industry requirements. That group was made up of several major pharmaceutical manufacturers and become the GAMP® Forum. In 2000, GAMP® became formally affiliated with ISPE as a technical sub-committee within the organization.



The guide has been broadened to incorporate a closer relationship with the ideals of system validation. The following sections identify the top-level features of the GAMP® guide.

## Validation Overview

Validation is applied to many aspects of pharmaceutical manufacturing, including instrumentation, systems cleaning etc. In each case the objective is to produce “documented evidence, which provides a high degree of assurance that all parts of a facility will consistently work correctly when brought on-line”. Traditionally, validation has consisted of the following:

Design Qualification (DQ) - Documented evidence that the design of the system meets requirements

Installation Qualification (IQ) - System has been installed correctly

Operational Qualification (OQ) - System operates according to design

Performance Qualification (PQ) - System meets design criteria, and operates according to requirement

Traditionally, each of the ‘Qualification’ sections has contained both the specification and the test protocols aimed at verifying that each stage is completed. The term *Validation Protocol* is often used when referring to these documents.

The guide recommends the use of supplier documents, if suitable. Documents provided by the supplier will simplify the overall validation process. Many of the tests performed by suppliers meet (or exceed) the site requirements for IQ and OQ, and often become reference documents for the User to direct a testing matrix toward.

## System Documentation

The documentation for an automated system should follow the “V” model. This model shows how the three main qualification activities can be linked back to the design process. The V model principle works well for smaller straightforward systems, such as a monitoring system, which has little or no integration into site wide services.

The document which initiates the validation process is the User Requirement Specification (URS). This describes the equipment or system as it is supposed to work and is normally written by the system user. The original version issued for quotation should normally contain the essential requirements (musts) and the desirable requirements (wants). The final version then accommodates all the musts, which can be met, and any of the wants, which also can be satisfied. The URS is now a standard document required for companies to meet the ISO9001: 2000 standards.

The Function Design Specification (FDS or FS) is normally written by the supplier and describes the functions of the equipment or system. The FDS links to the OQ as each major parameter stated should be tested. The FDS is also a standard output document required by ISO 9001: 2000.

The documentation then includes the system build and testing of the installed components. These documents are the testing qualifications IQ, OQ and PQ. At given stages during the lifecycle of the project, planned and systematic reviews should be performed. The design reviews evaluates the deliverables against standards and requirements. The overall validation lifecycle is therefore:

<b>Development Activities</b>		<b>Validation Activities</b>
User Requirements Specification Functional Specification	Planning and Specification	Validation Plan Supplier Assessments Design Reviews
Hardware Design Specification Software Design Specification Network Design Specification Package Configuration Specification	Design	Design Reviews
Hardware Manufacture and Assembly Code Software Modules Network Manufacture and Assembly	Construction	Construct Reviews Code Reviews
Hardware Testing Software Module Testing Software Integration Testing Package Configuration Testing	Testing	Monitor Supplier (Testing done at this level can contribute to IQ/OQ)
Hardware Installation Software Installation Network Installation Hardware Acceptance Testing Network Acceptance Testing	Installation	Installation Qualification
System Acceptance Testing	Acceptance Testing	Operational Qualification Performance Qualification
Maintenance Change Control	Operation	Validation Report Maintaining the Validated state

### **Maintaining the Validated State**

When a system is validated and in operation, measures should be taken to ensure that the system remains in a validated state. This maintenance not only involves the integrity of the hardware and software, but also the documentation. The maintenance of a validated system includes many activities, which the User is responsible for.

### **System Operational Procedures (SOPs)**

SOPs should be established to define the use and support of the automated system. SOPs should be approved prior to use.

## **Training**

Training plans should be established for use and support of the system. These plans need to consider the training of all users, technical and support.

## **Problem Management & Resolution**

How the faults in the software / hardware are initiated, reviewed, prioritize, and closed.

## **Service Agreements**

All service agreements should provide a formal approach to the support of an automated system. It should be unambiguous, define how the service is to be provided and provide a means of measuring the performance of the support.

## **Backup and Recovery**

How the system is backed up, where the copies go, and at what frequency the archives are made.

## **Configuration Management**

Procedures to establish the baseline system (close of Validation), control of configuration (workarounds and patches), ensure the completeness of changes, control and storage of the revised items.

## **Operational Change Control**

All changes proposed during the operational phase should be subject to formal change control processes.

## **Security Management**

Automated systems and data should be protected against willful or accidental loss or damage. The regulations for 21 CFR 11 surpass the outlines given in GAMP® 4.

## **Performance Monitoring**

The impact of system failure will vary depending on the criticality of the automated system. Where possible, monitoring of the performance of the system should be done to capture problems in a timely manner.

## **Record Retention & Archiving**

SOPs for the retention archiving and retrieval of data should be established and documented.

## **Business Continuity Planning**

This is aimed at disaster recovery and contingency plans should a system fail. Topics include catastrophic failure of either the software or hardware and alternative means of manufacturing.

## **Periodic Reviews & Evaluation**

These are done to verify that a system remains in a validated state and is being operated in accordance with SOPs.

## **System Retirement**

Due to the volume of data, decommissioning a system can be a major task. Considerations should be given to a procedure to replace the system, retained records, which GxP records are required, migration of data to new systems, retention of old hardware to be able to read the records and system archiving.

## **Validation Lifecycle**

Any system requires cooperation between suppliers and users. It is beneficial if the supplier uses a formal management system to control documentation, including the production of the software package. Users should verify that the documentation supporting the project lifecycle meets the company expectations; this is usually done via a supplier audit.

Each company should have a defined policy regarding automated systems. A site wide Validation Master plan should identify the following User Responsibilities.

### **Identify System**

Each system should be assessed and GxP systems identified

### **Produce URS**

This should clearly define precisely what the user wants from the system.

### **Determine Validation Strategy**

Includes sections on:

- Risk Assessment: Does the system require validation? How much validation is required? What aspects of system or product safety are at risk? What aspects of the system are critical to business?
- System Components Assessment: The categorization of the software and hardware components.
- Supplier Assessment: A formal assessment of each supplier; company audit. The audit may establish that a supplier has a quality system ISO9000 and in which case this may be given as reason not to perform a site audit.

### **Validation Plan**

Document defines activities, procedures and responsibilities of the project, and identifies the areas for Risk Assessment. Also included are Quality Plan and Project Plan.

### **Review/Approve Specifications**

The user must review and approve all specifications from the supplier, including the Functional Specification and detailed hardware and software specifications.

### **Monitor System Development**

The user should monitor the project in line with milestones.

### **Review Source Code**

Source Code should be adequately reviewed. This includes reviews of all development tools, policies and procedures, programming rules and testing.

### **Review/Approve Test Plans**

The user must approve test plans prior to formal testing.

### **Perform Testing**

The user may be used as a witness or tester for the software module & integration testing and the Hardware & System acceptance testing.

### **Review Test Reports**

The user should approve the test outputs from the formal testing.

### **Product Validation Report**

The Validation Report should summarize all the deliverables and activities and provides evidence that the system is validated.

### **System Retirement**

The user should manage the replacement or withdrawal of the system from use.

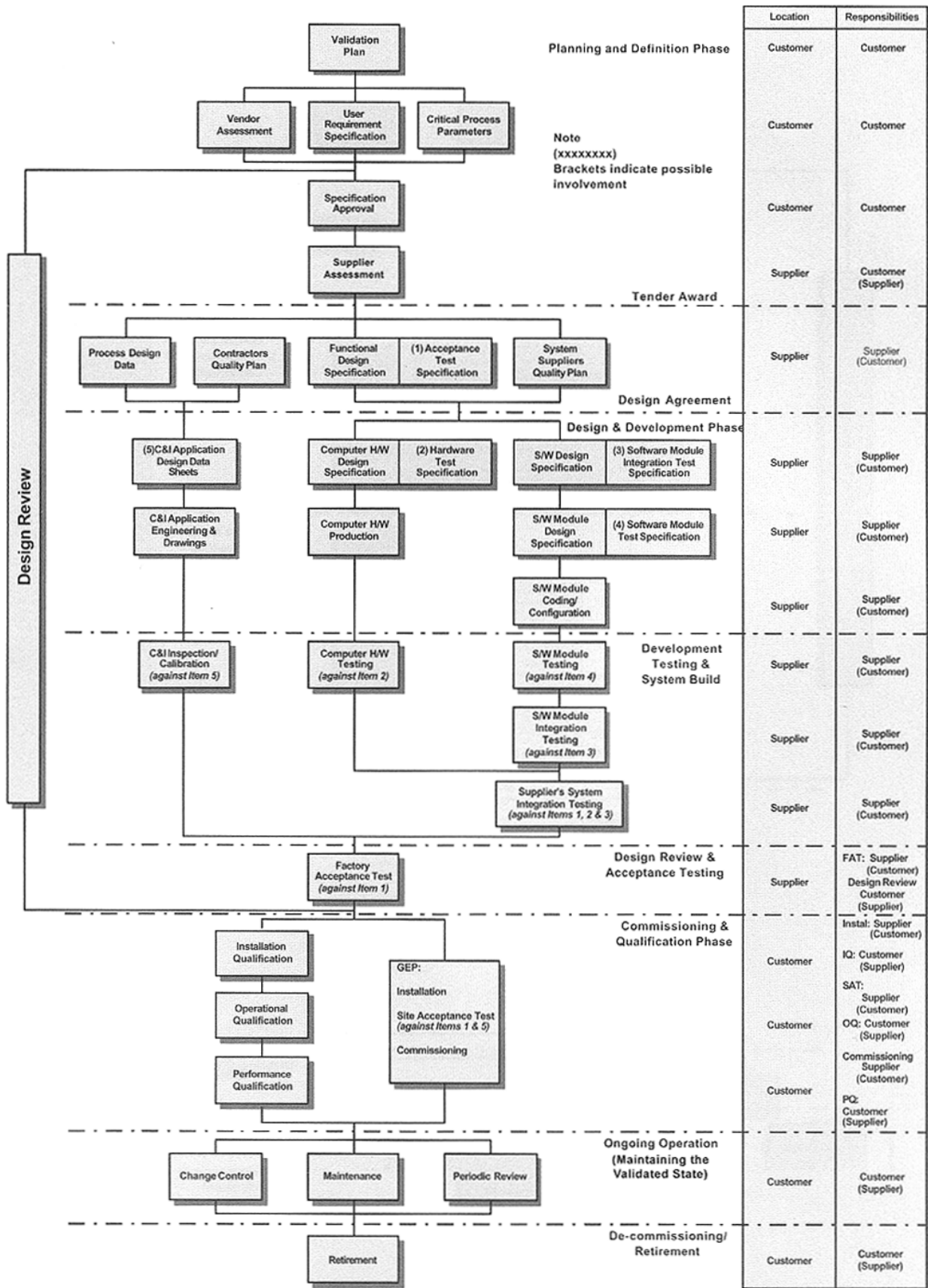
Two types of system are identified in the guide are:

#### **IT Systems**

Database packages, such as LIMS and MRPII fall into this category, it is where data is stored either fixed analytical or documentation.

#### **Process Control Systems**

Control systems, Monitoring systems and analytical systems fall into this category.



## Lifecycle Validation

The guide differentiates between *Embedded* and *Standalone* process control systems.

**Embedded** systems are microprocessor based systems such as programmed Integrated Circuits (IC), Programmable Logic Controllers (PLC) or PC with the sole purpose of controlling or monitoring a piece of manufacturing or analytical equipment; examples are filling machines, packaging machines and particle counters.

**Standalone** systems are either custom or configured, self-contained systems, which are components of an automated manufacturing process application. They are delivered as free standing computer systems, separate to the plant equipment. Examples of standalone systems are:

- Multi-loop controllers or PLCs controlling part of a process

- Supervisory Control and Data Acquisition (SCADA) systems (*Pharmaceutical Net fits here*).

- Distributed Control Systems (DCS)

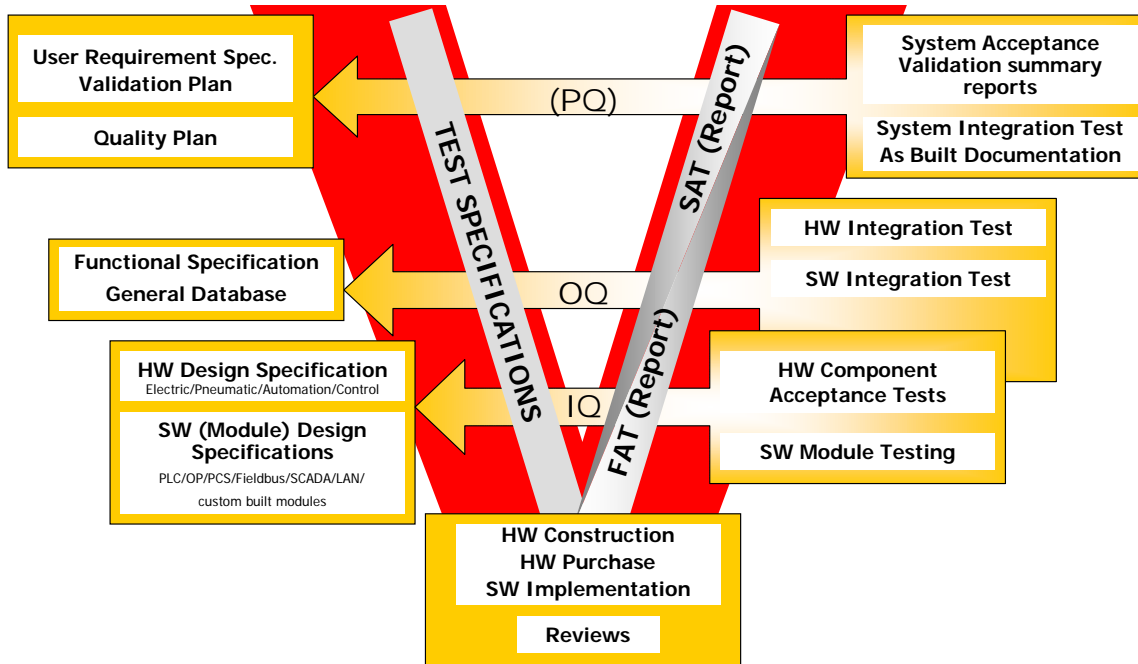
- Building Management Systems (BMS)

The pre-requisites for validation at minimum costs for both types of system are the same, following the same basic principals to system lifecycle.

## Planning

# *The GAMP 'V' Model*

## V - MODEL for Specifications, Build and Testing



During the planning phase the user assesses the supplier's quality system. The supplier should develop a Quality and Project Plan. The planning phase may include or relate to mechanical and electrical activities as well as automation. The supplier should assist with the Risk Assessment, reviewing the potential impact of system failures.

### Specification and Design

#### User Requirements Spec (URS)

The URS for large systems may involve the development of separate URSs, which cover all the different elements of the project. The manufacturing parameters to be controlled or monitored and the data to be generated should be clearly documented. The design and testing of hardware and software components affecting product criticality should be assessed.

#### Functional Spec (FS)

The FS is normally written by the supplier and describes the detailed functions of the entire system, what the system will do. The FS is a contractual document and should be subject to change control.

### **Detailed Design Spec (DSS)**

The detailed design includes the production of the hardware, software and instrumentation. It should specify equipment schematics, Process & Instrument diagrams (P&ID), Loop schedules, Process sequences and interconnection drawings.

### **Hardware Design Spec**

This document defines the architecture and configuration of the hardware, including computers, hubs, instrumentation, vacuum pumps, alarm devices etc.

### **Software Design Spec (SDS)**

The software design document (SDS) should define how the software implements the requirements of the FS. The SDS should define the logical and physical structure of the software program and the standards for the build.

### **Instrument Spec**

The system components should be organized into a document, which makes it easy to add and move sensors around the system.

### **Development and Build**

The development activities for the system should be based upon the appropriate design documents. There are three main activities, Software Development, System Build, and Production of Engineering drawings.

### **Design Review**

A design review involves planned and systematic reviews of the system design and development throughout the life cycle. It evaluates deliverables against standards and requirements. The process involves verifying that hardware tolerances and performance meet the requirements. The outcome of any review should be documented on a Design Review Report.

### **Software Development**

The supplier should establish and maintain a formal system for controlling software production.

### **System Build**

For a standalone system the software, instrumentation, and regulating devices are shipped to site, inspected and installed, with the manufacturing plant equipment.

### **Software Review**

The supplier should ensure that the software has been properly inspected and reviewed prior to shipment. The version shipped to site should be the final available release. Suitably qualified persons should perform reviews.

### **Supplier Testing**

The tests should demonstrate that the design conforms to the requirements of the system.

### **Development Testing**

This covers four areas, Software Development tests, Hardware Manufacturing Tests, Software and Hardware Integration Tests, and Instrument and Electrical Equipment manufacturing Tests

### **Acceptance Testing**

These tests are normally contractual milestones aimed at proving the correct operation of the system. Testing should be based upon an approved System Acceptance Tests Specification and formally reported and reviewed. The system type and complexity all influence the degree of testing required. Testing at the supplier's facility prior to shipment is referred to as the Factory Acceptance Tests (FAT). For a standalone system the tests are performed without the installed cabling and may include a reduced system capability. Site Acceptance Tests (SAT) are then performed to verify that the system has been shipped without damage and meets the site requirements form functionality.

The SAT may be combined with equipment and plant commissioning; this provides the basis of the IQ/OQ for the plant. This incorporation of SAT into qualification testing is acceptable where the level of detail and documentation of the system meets the site requirements for IQ/OQ.

### **Instrument Calibration**

Calibration and maintenance of instrumentation should be performed to approved procedures.

### **Qualification**

Qualification activities formally verify the suitability of Process Control Systems for use in a facility.

IQ confirms that the software has been installed correctly, specified hardware components have been assembled and installed correctly, power supplies and data communications are installed correctly and basic power up functions operate.

QO confirms the system operates per the FS. Including software and hardware functions under normal load and where appropriate under realistic stress conditions.

PQ confirms that a system is capable of performing or controlling the activities of the process, while operating in a specified environment.

## **Validation Report**

On successful completion of system qualification, a Validation Report confirms that the system is ready for use within the process for which it was originally designed. PQ for a PCS system is usually conducted in conjunction with Process Qualification, i.e. over an extended period of time opt verify integration into other systems.

## **Maintaining Validation**

The User should establish and maintain plans for continued validation. See section 2.3 above.

## **Retirement**

At the end of operational life a system should be decommissioned.

## **Benefits of Validation**

Validation is the formal documentation of good system development practices. The principal benefit of validating a system is *Compliance*. The information gathered before, during and after validation leads to improved and confirmed compliance as changes are introduced. Other benefits are:

- Systems which are well defined and specified, easier to maintain, resulting in less downtime

- The system delivered is fit for purpose, on time, within budget

- Satisfy the User Requirements

- In-depth understanding of the process

- Improved operational efficiency in a shorter time frame

- Reduced risk of failure

- Maintenance of quality standards

- Operators understanding the systems, leading to improved communications between departments

## **List of Appendices in GAMP® 4**

The appendices of the GAMP® guide is where all the detailed descriptions as to how processes or more detailed guides to particular application exists. The appendices are divided into three sections, Management, Development and Operations. The management appendices are used for project planning and system requirement analysis. The Development appendices are used for the production of documentation allowing for a detailed description, Hardware and Software, of the system to be installed. The Operational appendices are used for the maintained validation of a system. The Development appendices are directed at suppliers where as the other, Management and Operations, are directed at the user. This is a significant development from the original GAMP® guides, which were solely aimed at suppliers.

## Management Appendices

Appendix No.	Title	Summary
M1	Guideline for Validation Planning	Used for the production of a VMP and individual VP for systems and projects. It details the validation required to complete a project.
M2	Guideline for Supplier Audit	Used to construct the different types of supplier audit (internal Audits, 2 <sup>nd</sup> party audits and 3 <sup>rd</sup> party audits) and the differing methods of performing these audits.
M3	Guideline for Risk Assessment	Describes a simple Risk Assessment process that might be applied to systems. Purpose is to avoid risk to patients, maximize benefits from a system.
M4	Guideline for Categories of Hardware and Software	Defines the 5 categories for software Operating Systems Firmware Standard Software Packages Configurable Software Packages Custom (Bespoke) software  And the 2 hardware categories Standard Hardware Components Custom Built Hardware Components.
M5	Guideline for Design Review and Requirements Traceability Matrix	Outlines how a design review is performed and construction of a traceability matrix.
M6	Guideline for Quality and Project Planning	Document defining the supplier quality system, responsibilities and project milestones.
M7	Guideline for Validation Reporting	Describes the Validation reporting process, activities involved, responsibilities of the parties and how the report can be used.
M8	Guideline for Project Change Control	Guideline for the changes to a system, as it passes from development into production. The Supplier manages project change control.
M9	Guideline for Configuration Management	Defines the activities required to a configurable system for the lifecycle of a system, identify the baseline, record the status and changes, control and

		storage of system.
M10	Guideline for Documentation Management	Defines how Good Documentation Practice should be performed. Contains a series of templates for use.

### Development Appendices

Appendix No.	Title	Summary
D1	Example Procedure or the production of a URS	Defines the major components and sections of a User Requirement Spec.
D2	Example Procedure or the production of a Functional Specification	Defines the major components and sections of a Functional Spec, All sections should be present, where the system does not fit the section should be marked 'NOT APPLICABLE'. Should reference the sections of the URS.
D3	Example Procedure or the production of a Hardware Design Spec	Defines the major components and sections of a Hardware Design Spec, it should also have references back to the FS.
D4	Example Procedure or the production of a Software Design Spec	Defines the major components and sections of a Software and software module design specification.
D5	Guideline for the Production, Control & Review of software	This document identifies the major components of the software production, control and review document; It highlights areas as design principles, traceability, maintainability and source code reviews.
D6	Guideline for Testing of an Automated System	Defines the major components and sections of a test specification. Describes the elements of a system that the test specification needs to address, verification against deliverables, GxP compliance, alarm tests, critical functions, start-up & Shut down, back-up & Recovery and disaster recovery.

### Operational Appendices

Appendix No.	Title	Summary
O1	Guideline for Periodic Review	Used to perform periodic reviews, timing a&

		scheduling, the preparation of the review and conducting the review.
O2	Example Procedure or the production of a Service Level Agreement	Describes the elements of a SLA. The responsibilities of parties, the description of the service requirements, including prioritization, software patches & upgrades, calibration and repairs. It also defines the measurement and reporting (ISO9000) and reviews.
O3	Guideline for Automated System Security	Defines the sections of a security policy, all system should have an OWNER. Document defines system classification, responsibilities, and employee awareness and physical security. 21CFR11 has surpassed the requirements defined in this appendix.
O4	Guideline for Operational Change Control	Defines the scope of change control. Identifies the mechanisms, which allow changes to be implemented within a validated framework.
O5	Guideline for Performance Monitoring	Identifies the parameters to be monitored for performance, servers and computers, networks, applications, instrumentation. Also defines the notification mechanisms and performance reviews.
O6	Guideline for Record Retention, Archiving and Retrieval	Defines the requirements for the retention, archiving and retention of GxP records, including hardcopy reports as well as softcopy reports. It identifies many different types of report including, product, batch, complaint, training, adverse drug effects and audit records. It gives guidance to record retention in secure facilities, and when archiving is required. Record retrieval procedures are identified, authorization of removal, human readable from electronic data issues are raised.
O7	Guideline for Back-up and Recovery of Software and Data	EU Guidelines “ <i>data should be protected by backing-up at regular intervals. Back-up data should be stored as long as necessary at a separate and secure location</i> ”. The document identifies questions, which need to be answered to produce a reliable back-up procedure.
O8	Guideline for Business Continuity Planning	Defines the major components and sections of a business continuity plan. It covers what areas need consideration when looking at disaster recovery and

		avoidance.
O9	EU Guideline for Computerized systems with APV Interpretation.	The document is a published EU guideline on computer validation. It follows the GAMP® guide but is directly applicable to the User to comply to. However it is also the responsibility of all system suppliers to meet the requirements. If a system follows GAMP and Good Documentation Practice it would also satisfy the guideline.

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Technical Note 26  
2002  
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