

Lighthouse Monitoring Systems and GAMP5 Overview

by Jason Kelly and Michael Chunhan

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What is GAMP?

Good Automated Manufacturing Practices (GAMP). GAMP is both a technical subcommittee of the International Society for Pharmaceutical Engineering (ISPE) and a set of guidelines for manufacturers and users of automated systems in the pharmaceutical industry. ISPE is the world's largest not-for-profit association serving its members by leading scientific, technical and regulatory advancement throughout the entire pharmaceutical lifecycle.

ISPE was founded in 1980 by a handful of people who believed the pharmaceutical industry needed an organization that would deal with practical applications of science and technology for technical professionals.

GAMP is a set of guidelines for manufacturers and other automation users follow to maintain operational efficiency and reliability. The goal of GAMP is to promote the understanding of the regulation and use of automated systems within the pharmaceutical industry. The most well-known is The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems in Pharmaceutical Manufacture. The last major revision (GAMP5) was released in February 2008.

Other publications in the GAMP series include;

- GAMP Good Practice Guide: A Risk-Based Approach to Compliant GxP Computerized Systems
- GAMP Good Practice Guide: Calibration Management
- GAMP Good Practice Guide: Electronic Data Archiving
- GAMP Good Practice Guide: Global Information Systems Control and Compliance
- GAMP Good Practice Guide: IT Infrastructure Control and Compliance
- GAMP Good Practice Guide: Testing of GxP Systems
- GAMP Good Practice Guide: Validation of Laboratory Computerized Systems
- GAMP Good Practice Guide: Validation of Process Control Systems

GAMP itself was founded in 1991 in the United Kingdom to deal with the evolving U.S. Food and Drug Administration expectations for good manufacturing practice (GMP) compliance of manufacturing and related systems.

GAMP published its first guidance in 1994. Soon afterwards the organization entered into a partnership with ISPE, formally becoming part of ISPE in 2000. GAMP has enjoyed the support of numerous regulatory authorities over the years spanning the United States, Europe, and Japan and is now a recognized good practice worldwide.

Understand GAMP 5

The acronym GAMP-5 refers to "Good Automatic Manufacturing Practices issue 5", document. Production systems for the pharmaceutical and food industries have to comply with ever-stricter legislation, including regulations of the European Medicine Agency (EMA) and Food & Drug Administration (FDA). Although Good Automated Manufacturing Practice (GAMP) is not a mandatory legislation, it provides important guidelines for companies involved in the development and/or implementation of automated systems.

GAMP 5 can be regarded as a structured approach for the validation of automated systems. Currently, version 5 of GAMP has a definitive status, with no version 6 in the pipeline. Compared to previous versions, the emphasis is more on risk control and quality management.

By correctly interpreting and applying the GAMP 5 guideline, companies working in regulated industries can ensure automated systems quality. It also becomes a lot easier for them to pass audits and government inspections.

How does Lighthouse apply GAMP5 into their Lighthouse Monitoring Systems software?

At Lighthouse we have and maintain an excellent Quality Management System and our Engineering department follows our quality standards, develops and designs monitoring software based on our internal quality system and GAMP5 standards. Lighthouse has two main monitoring systems software programs both used in thousands of cleanrooms around the world. These software packages can be defined as Computerized Systems. This Lighthouse Monitoring Software (LMS) is (1) LMS Pharma/Pro and (2) LMS Express and they both follow a software development methodology in-line with GAMP5 guidelines.

Combining the best practices of the two methods (or models "Waterfall and Agile"), the team is able to deliver products of supreme quality, at no compromise to its business and customer needs while maintaining compliance to various regulatory standards, key ones to mention being ISO 9001:2015, GAMP 5 and Annex 11.

Software Development Life Cycle (SDLC)

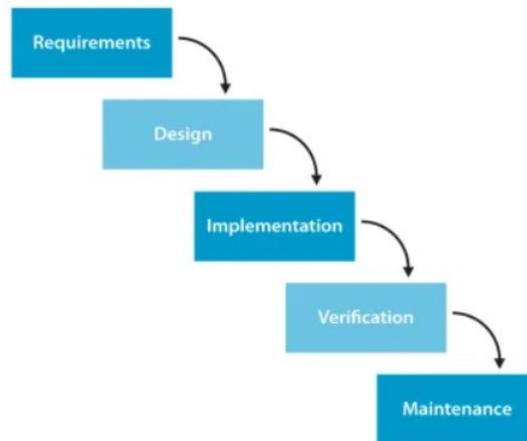
A Software Development Life Cycle (SDLC) adheres to important phases that are essential for software development such as planning, analysis, design and implementation. A number of SDLC models have been created overtime, the oldest and most widely used being the classic 'Waterfall' model.

The waterfall model is a sequential design process, in which progress is seen to flow downwards (like a waterfall) through the phases of Requirements Specification, Design, Implementation (Coding), Testing, Release and Maintenance. The model maintains that one should move to a phase only when it's proceeding phase is completed.

As any given process or model has its Pros and Cons, 'Waterfall' model has its own. While the model stresses the end product quality, its rigidity and inflexibility pose a challenge to meet changing customer requirements and market competition.

Key attributes of Waterfall Model:

- Detailed documentation.
- Agreed and Signed off Requirements, Design Specs and all other documents part of the cycle.
- Reduced number of defects through thorough planning.
- Defined start and end point for each phase, allowing progress to be easily measured.



Agile Development

Agile Software development can be viewed as an iterative and incremental development, where requirements and solutions evolve through collaboration between self-organizing, cross functional teams.

While it promotes adaptive planning, teamwork and collaboration, evolutionary development and delivery, and encourages rapid and flexible response to change, quality concerns are a primary drawback in safety-critical industries or industries where projects require heavy documentation and modeling before coding begins. And since waterfall development stresses the end product over process, it has remained prominent in these industries where quality (and safety) over speed reigns supreme.

At Lighthouse Worldwide Solutions we employ certain key principles of Agile Manifesto alongside the traditional waterfall model, the team is able to deliver best in class products to the market in reasonable amount of time.

Principles of Agile Manifesto as adopted by Team:

- **Total Customer Satisfaction:** High Priority to Total Customer Satisfaction (both internal and external). This is achieved by actively involving the internal customers (sales, marketing, service, Sr. management...etc.) in all phases of development there by providing an interactive platform to ensure products delivered meet the customer needs. Consistent involvement, feedback and approvals at all stages of development are achieved through the review process and records in place.
- **Iterative development of the requirements:** Frequent intermediary QA builds are released for testing of functionality, which helps identifying defects earlier in the development phase. This ensures that maximum test coverage for each new feature developed and regression of old features is achieved. And as such reducing the total

cost of development and time for product realization. Other key benefits include longer run time, fewer bugs escape, and test functions more than once

- **Pair Programming:** Pair programming is advocated, by assigning features to not just one programmer but two or more. This mitigates the resource in-sufficiency risk that can at times have a huge impact on project delivery and costs.
- **Welcome changing requirements, even late in development:** By employing a well-defined change management process, the team is able to effectively address any changes and/or additions to planned requirements, late in development. The Change Management process ensures that the change is well documented and that the change has been addressed appropriately and rapidly.
- **Collaboration between cross-functional teams:** Regular meetings are held at each stage of the development process (requirements review, design reviews, code reviews...etc.) between different teams. These meetings facilitate not just design reviews, but also the risk assessment and management.
- **Highly motivated individuals:** with commitment to project delivery and continuous learning.
- **Continuous attention to technical excellence and good design:** This is achieved through periodic design reviews with the project team and a Subject Matter Expert. All these review are documented to support the Quality of the Product.
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The resultant hybrid model of the “Waterfall and Agile” approach perfectly fits the V-model proposed in GAMP5, the Good Engineering Practices outlined in ASTM e2500, the requirements outlined in ISO9001:2008 and Annex 11.

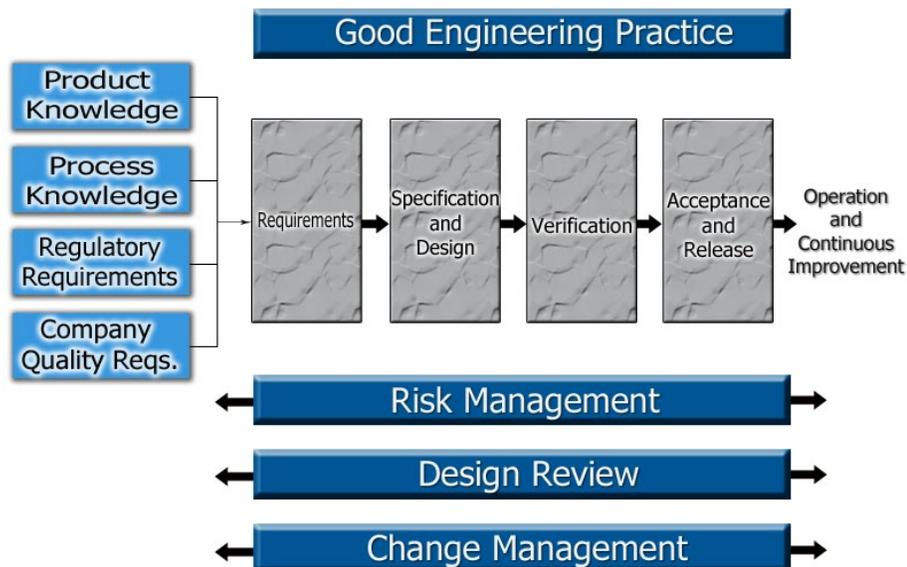
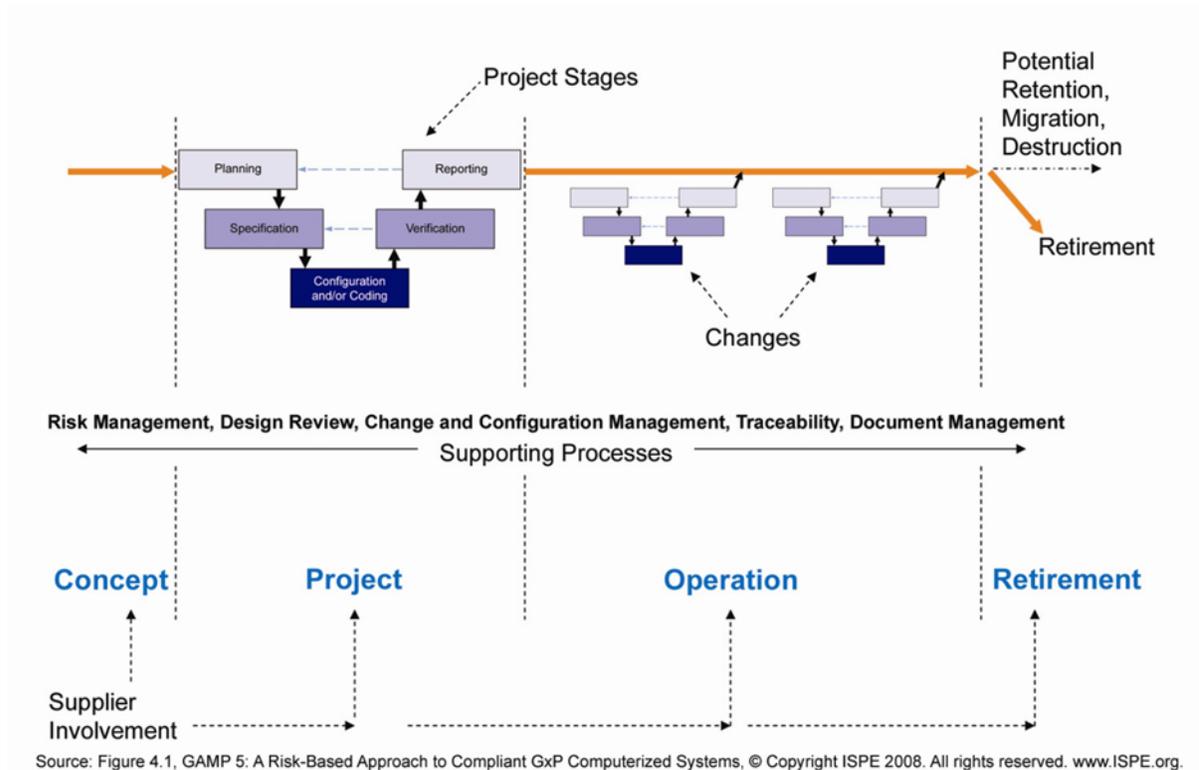


Figure 1 - Good Engineering Practice as outlined in the ASTM E2500.

ISPE, GAMP® 5, A Risk-Based Approach to Compliant GxP Computerized Systems states:

There are major business benefits in having a defined process that delivers systems that are fit for intended use, on time, and within budget. Systems that are well defined and specified are easier to support and maintain, resulting in less downtime and lower maintenance costs.



Source: Figure 4.1, GAMP 5: A Risk-Based Approach to Compliant GxP Computerized Systems, © Copyright ISPE 2008. All rights reserved. www.ISPE.org.

Figure 2 – GAMP 5 V-Model

The GAMP5 Validation Process

The range of activities required to validate a computerized system are determined by its GAMP 5 software and hardware categorization, GxP impact, applicable electronic records and electronic signatures requirements, and its risk-based lifecycle approach.

There are four life cycle phases of a computer system which are employed by GAMP 5 - concept, project, operation and retirement. Various activities take place in more than one phase, hence a fifth phase, multi-phase, is documented here to describe these cross phase activities.

1. Concept Phase

System Software and Hardware Categorization

The following GAMP 5 software and hardware categories are used to establish the validation approach and determine the deliverables:

GxP Impact Assessment

The GxP impact assessment is carried out to determine if the computer system has an impact on product quality, patient safety or data integrity. All GxP impact computer systems

must comply with applicable regulatory requirements and should have systems built in so the computer system (Monitoring Software) has service level agreements which keep the system running to its full potential and mitigate against down-times other than for planned events live systems service. Unplanned events need a fast response using vendor technical support or in-house technical support to make sure the system is redundant and manageable. At Lighthouse we offer SLA's with fast and efficient response time using remote support programs to ensure your system is given a priority service and to keep downtimes around unplanned events to a minimum.

GAMP Class	Category	Validation Action
1	Operating Systems	Record ID and Version.
2	Instruments and controllers	Record configuration and calibration.
3	Packages where existing code can be selected and set points imputed.	Audit supplier – validate any bespoke code – validate functionality
4	Systems that the code or part of the code are configurable.	Audit supplier and code, validate any bespoke configurations apply full life cycle requirements.
5	Systems utilizing custom or bespoke code which produce predicate rules information.	Audit supplier, validate all code, apply full life-cycle requirements

Figure 3 – GAMP 5 Categories and Level of Validation

*LMS Pharma/Pro and LMS Express RT follow GAMP Class Category 4

Electronic Records and Electronic Signatures (ERES) Assessment

An assessment is carried out to establish if the system needs to meet the requirements of electronic records and electronic signatures by determining what electronic records are created by the system, how those records are maintained and how the records will be signed, either by hand or electronically. By using a traceability matrix to ensure the system design and system support meets these requirements the assessment becomes more simplified. Always remember a Monitoring System vendor can never provide a 100% 21CFR11 compliant system. There are user requirements to follow under 21CFR11 guidelines that are out of control of the vendor and the end user needs to know how to manage these user requirement segments of 21CFR11. By working with your Monitoring System vendor these responsibilities can be identified and planned for in the validation phase.

2. Project Phase

Supplier Assessment

Monitoring System suppliers should be audited to verify their capacity in providing and maintaining a reliable system. Lighthouse hosts regular external audits where our Quality Management System and System and Software Life Cycle (SDLC) are reviewed. Some assessments occur onsite and some assessments are conducted remotely depending on the Customer's Risk Assessment.

Risk Management

There are many guidelines on risk assessments and GAMP5 guidelines recommend the risk assessment to be performed at various key stages of the validation process by a team who fully understand all the processes and requirements. Subject Matter Experts (SME's) may be engaged if internal resources do not have the technical team.

These consultants can help the team put together a formal system risk assessment and the earlier this team engages the better outcome the project will have. From the risk assessment a more robust User Requirement Specification (URS) can be developed.

A functional risk assessment is performed following approval of the functional specification to identify potential risks. Mitigation activities are then planned to manage the identified risks and allow focusing on critical areas, e.g. by modifying functionality, detailed testing, procedural controls or training

Further risk assessments can be performed during the course of the project such as testing and deployment, and for other activities throughout the life of the system.

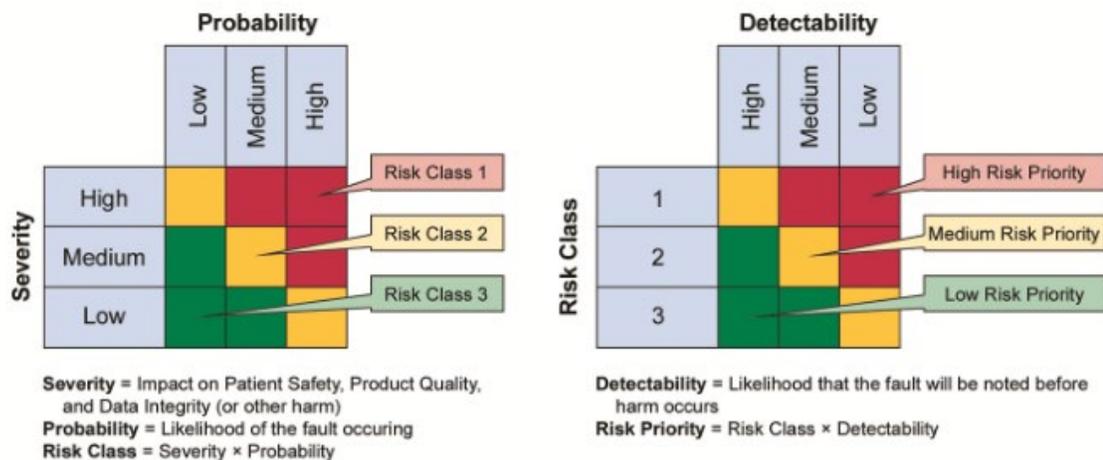


Figure 4 – GAMP 5 Risk Assessment Approach to Compliant GxP Computerized Systems

Validation Master Plan

The Validation Master Plan (VMP) defines the validation approach. It outlines and describes the activities and acceptance criteria and also lists the deliverability's and responsibilities. In developing the Validation Master Plan extremely important commitments and decisions have to be made.

Program conceptions have to be mated to the User Requirements Specifications (URS), From these plans the User Requirements Specification (URS), the Validation Risk Assessment (VRA), Functional Requirement Specification (FRS), the Design Qualification (DQ), the Installation Qualification (IQ), the Operational Qualification (OQ), and the Performance Qualifications (PQ) have to be developed and approved for content, and issued for execution.

The completed documentation has to be reviewed and accepted as complete by persons authorized to execute this role. All of these functions must be detailed in the Validation Master Plan, when the project concept demands that a VMP is required, or the Validation Plan (VP) where it does not. Responsibilities have to be declared, people have to be nominated, and everyone involved is duly served with a copy that carries the full authority of the company.

System Overview

The system overview is a brief description of the system and includes:

- System identification
- Business processes the system supports
- Data managed by the system
- High level functionality of the system
- High level schematic diagram of system architecture/hardware
- All interfaces to external systems
- How data is secured by physical or electronic means

The system overview may be incorporated into a section of the VMP.

What is a User Requirement Specification (URS)?

The URS outlines in table format the functions and features of the Monitoring System. It states what the end user of the system wants the system to do. The URS should be used to drive the development of the system functionality, configuration parameters, hardware and software design specifications and offer a traceability connection to the testing of the system. Factory Acceptance Test (FAT) and Installation and Operational Qualification (IQ.OQ) tests should all clearly indicate where they meet the URS requirements through testing and validation of the test outcomes. With the GAMP V model the URS sits at the start of the process.

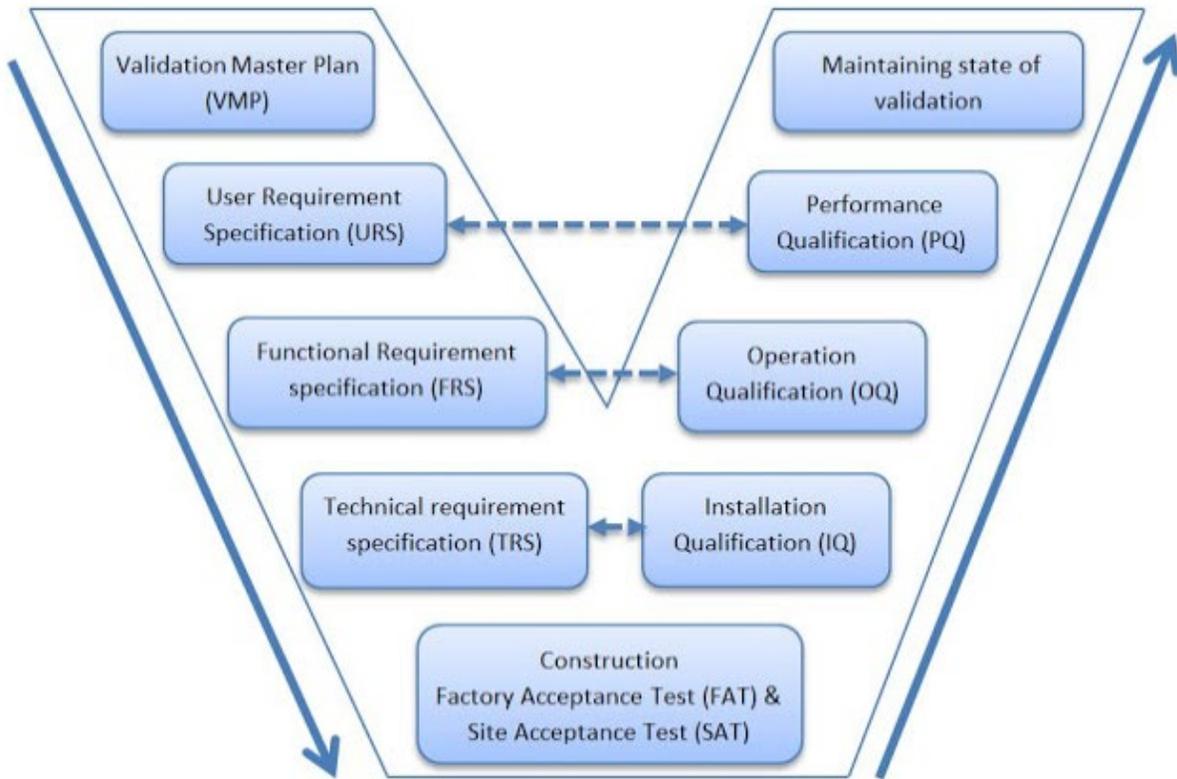


Figure 5 GAM5 V-Model

The Functional Requirement Specification (FRS)

The FRS defines the full system functionality including how the user and business requirements are satisfied. It is the basis for system design, customization, development and testing. The FRS is sometimes combined with the URS where the systems functions are outlined.

Technical Requirement Specification (TRS)

The TRS details the configuration parameters and how these settings address the URS. Sometimes referred to as the Configuration Specification (CS). The CS can be a standalone document or incorporated into the FRS. The TRS includes details regarding the hardware and software design. These documents can be further broken into the Hardware Design Specification (HDS) and the Software Design Specification (SDS) for larger systems.

Design Review (DR)

Although not outlined in the GAMP5 V model above the DR should be conducted before the Factory Acceptance or Site Acceptance testing documents or execution are

completed. The DR reviews the system design and verifies it meets required standards and the URS requirements and these requirements are traceable. If the system has specific software code developed the DR will also cover this to detect and rectify coding errors. The output from the risk assessment is also part of the DR. The factory testing, site testing installation verification, functional verification and requirements verification testing documents are generated against pre-approved specifications. Test cases are written in test steps as instructions to be followed to test whether the system satisfies the defined acceptance criteria appropriate for the test level. The test steps are written in sufficient detail so that testing is repeatable with consistent results. The design review report documents the outcome of the design review process.

Factory Acceptance Test (FAT) and Site Acceptance Test (SAT)

The FAT is performed after the system has been built and before it is shipped onsite. The End User normally travels to the vendor's factory and witnesses the operation of the system. At this stage any system performance issues can be detected and rectified before the system is shipped to the customer site. The SAT is completed once the system arrives onsite and is installed.

Installation Qualification IQ

Once the Monitoring System has been through a FAT or SAT (*Note based on a Risk Assessment a FAT and SAT may not be required and the system can be installed and commissioned prior to the IQ) the Installation Qualification can be started. The IQ validation goes over the system and verifies all the deliverables in terms of physical parts of the system. This includes, sensors, software, servers, vacuum pumps, certification documentation, materials of construction documentation and such deliverables traced back to the URS. The IQ verifies that the system is installed as expected and the system is ready for the OQ to commence.

Operational Qualification OQ

The OQ is really the operational test and validation that the system meets the URS and design, functionality and operational requirements. Your vendor should drive this validation process but you the customer should participate and fine tune your Standard Operating Procedures (SOPs). All features, configurations and functions of the system are tested as well as 21CFR11 features and security functions of the software. The OQ should test the system running and in the operational state as well as the level of system redundancy and disaster recovery attributes. At this stage the end user should be thoroughly immersed and involved with the OQ. The OQ is also a good form of training and a stepping stone to finalizing the SOPs used to keep the system operational and how certain events are managed. Training on how the system is to be operated is critical and operators need to know how to run the system flawlessly. System Training SOPs should be fine-tuned here. The computerized system should be verified and

validated as fully operational and working in unison with SOPs specifically developed during the planning phase.

Performance Qualification PQ

The PQ is the end piece of the whole project phase. This is the last testing phase the monitoring system goes through before the system becomes operational and goes into a live process. The PQ should not be a regurgitation of the OQ. The PQ should set final challenges of the monitoring system and it should be run as if it were in an operational environment. Configurations such as alarm limits, redundancy and SOPs should all be tested and have final adjustments based on how the systems “performs” in this operational environment. How operators and management interact with the system, how SOPs are followed in this operational environment all should be carefully examined. This is the final time the system will be tested before going live so operator familiarity and the operator training should all be addressed here, tested and managed to the point of being flawless. The last thing a production manager or quality manager should have to face is a system that is not running smoothly and finding this out in the operational phase can be very costly and serious if drug supplies are affected.



Figure 6 Monitoring System Validation Testing

3. Operational Phase

Quality Management System updates

Before the operational phase is underway all system operating procedures, manuals, certificates of calibration and certificates of conformity need to be signed off and implemented in the Quality Management System. All operators and employees using the monitoring system need to be provided with the level of training suited to their responsibilities. Key users must be trained in the use of the system software and all remote connections should be tested and validated for performance and security. Service Level Agreements and support plans need to be in place and procedures defined to maintain the system in the validated state. Roles and responsibilities must be clearly defined. Follow EU GMP Annex 11 guidelines on Computerized Systems. For example has the system continuity been correctly provided for? How long would it take the system to be operational again if a module was to fail? Are there sufficient spare parts available off the shelf at your site to implement a plug and play turnover? Did your vendor supply a spare parts BOM prior to handover? More importantly you should have purchased one. Has your team of maintenance technicians been sufficiently trained to maintain the system sufficiently and with efficiency? All these questions need to be answered and you need to ensure your business continuity. If a monitoring system goes down how quick can it be operational again and how much is your company losing by the hour when the system goes down?

Validation Report (VR)

Once the PQ has been successfully implemented and signed off the system must be documented as released with details outlined such as date of release, system version, department and owner of the system. A validation report should be developed outlining the activities of the project life-cycle where any documented deviations observed during the testing outlined with the corrections made to the system followed up with retesting verification. The Validation Report (VR) should include a statement which summarizes the testing and implementation of the system.

System Data Integrity and Control

Backup and restore routines should be operational based on the risk assessment in terms of frequency. Data should be protected and readily available when required and stored in secure data files on secure servers. All data should be verified as incorruptible in its original format. Data archiving should be implemented when the data is no longer actively used. All data must be retained for regulatory inspections and compliance. Backup and Restore, Data Archiving and Retrieval should be clearly proceduralized in SOPs.

Periodic Review

The ongoing performance of the system must be regularly checked. Periodic reviews are performed to ensure that the computerized system remains within compliance and is fit for its intended use. For example are the configured alarm limits working well? Should

they be increased or decreased based on system performance? If so all configuration changes should follow a well-documented change control process.

Change Control Management

Change control should be implemented throughout the whole system process from Concept, Project, Operational and Retirement phases. The change management process defines the requirements for assessing, documenting and managing changes to ensure systems remain in a validated state and applies to software, hardware, configuration data and documentation.

The process requires all planned and unplanned changes to be planned, assessed, executed and closed in a controlled and compliant manner. Project change control is used to manage changes made to any approved primary design documents, project scope changes or changes that will have an effect on product quality, patient safety, data integrity, project cost or schedule.

Incident management and any system deviations for the entire system lifecycle also need to be managed for any incidents that may affect the quality of system data. Incident logs should be maintained and be managed effectively. All deviations must be investigated and root causes and fixes identified and any changes to enable fixes must follow the change control process and be firstly tested to ensure the fix works and the fix does not affect any other part of the system. Any changes to the system must also be reflected in the system documentation. Configuration documents need to be updated and revised and put through the QMS. System access and security management needs to be retested after any changes made. A risk assessment of any changes will need to be developed and define what parts of the system require revalidation due to the changes made.

4. Retirement Phase

Decommissioning

A decommissioning plan must be prepared for systems that are to be retired from operational service so that the process is documented and controlled. Consideration must be taken into account with regards to the archiving of data and records retention requirements, along with any hardware disposal. If the system is to be replaced and upgraded with a more modern system then careful consideration should be taken for the transition of the new system and the business continuity impact.

Summary

GAMP5 standards are an essential part of software and hardware development and in the implementation of monitoring systems that use hardware and software to monitor the cleanroom environment. Lighthouse Worldwide Solutions embraces the spirit and drive for excellence through GAMP5.

As you can see when GAMP5 is put into practice and implemented the success ratios of projects involving Cleanroom Monitoring Systems increases. Companies that internally follow and implement GAMP5 produce higher quality and more reliable products.

Customers should audit their monitoring systems (computerized systems) suppliers carefully and verify their abilities and track records. Environmental Monitoring data is critical data and the integrity of that data is paramount. Starting such a project with the right steps and with the right level of resources is crucial to the success of the project. A badly or poorly executed project will result in a poor and unreliable monitoring system.

Customers themselves should also implement GAMP5 and have all the necessary resources in place and a strong QMS where all of the project lifecycle is well documented and implementation of SOPs and execution of them are validated thoroughly. Operator and Management training on the system is such an important process and there should be no excuse for missing out on system training. By all means leverage as much as possible from your monitoring system vendor but make sure your team is actively involved and are properly trained up on using the system and following SOPs which have been designed and validated through the whole process. Quality should be built into the process and GAMP5 enables a solid process to be developed and implemented.

