

Cleanroom Environmental Monitoring Systems, Regulatory Compliance, and Risk Mitigation

by Jason Kelly

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With the never ending shift towards continuous quality improvements within the manufacturing of pharmaceutical products it is worth looking at the current requirement of GMP and also 21CFR11 in the context of GAMP 5 requirements. How a Company creates, maintains, retrieves, corrects and controls data can affect product quality. How a company reacts to out of tolerance conditions via continuous Environmental Monitoring Systems (EMS) alarm notification is crucial to the process operation and the product quality. Therefore the EMS becomes a critical process tool to ensure product quality and the data itself.

As far as electronic records are controlled, the FDA's main concern has remained the same since the introduction of 21CFR11 and that is "to safeguard record integrity in order to ensure product quality". Therefore "record integrity and data integrity" is a focus by the FDA during regulatory audits. So it makes sense to have a robust EMS that can be validated confirming it meets the requirements of regulatory compliance and that means that Manufacturing Pharmaceutical companies should be looking closer at their Vendors to support them in the drive for these continuous process quality improvements.

More and more Pharmaceutical Companies are using Risk Mitigation practices in the selection of the right Monitoring System provider with the emphasis on strong validation support on going technical support to reduce down time and potential loss of production time which may lead to product shortages and loss of revenue. Therefore selection of the right Vendor is critical as it may impact on Business Continuity. Let's also look at other important topics apart from the EMS vendor that must be considered;

What is GMP?

Good manufacturing practices (GMP) are the practices required in order to conform to the guidelines recommended by agencies that control authorization and licensing for manufacture and sale of food, drug products, and active pharmaceutical products. These guidelines provide minimum requirements that a pharmaceutical or a food product manufacturer must meet to assure that the products are of high quality and do not pose any risk to the consumer or public [*Source FDA Good Manufacturing Practices*].

What is GAMP?

It 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. More specifically, the ISPE's guide The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems in Pharmaceutical Manufacture describes a set of principles and procedures that help ensure that pharmaceutical products have the required quality. One of the core principles of GAMP

is that quality cannot be tested into a batch of product but must be built into each stage of the manufacturing process. As a result, GAMP covers all aspects of production; from the raw materials, facility and equipment to the training and hygiene of staff. Standard operating procedures (SOPs) are essential for processes that can affect the quality of the finished product. Below is an example of the GAMP “V” model for EMS development, testing, validation and performance.

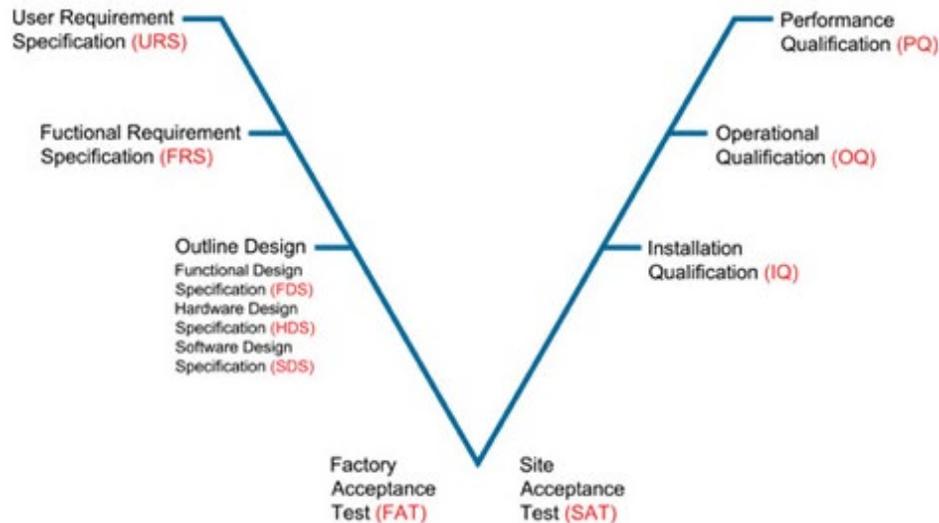


Fig.1 Factory Acceptance testing setup of a Monitoring System

What is 21CFR11?

Title 21 CFR Part 11 is the part of Title 21 of the Code of Federal Regulations that establishes the United States Food and Drug Administration regulations on electronic records and electronic signatures. Part 11, as it is commonly called, defines the criteria under which electronic records and electronic signatures are considered trustworthy, reliable, and equivalent to paper records

21CFR11 was initially released in 1997 there was much confusion in the Industry on the implementation and the requirements by manufacturers and vendors. In 2003 the FDA

released a Scope and Application update. In 2010 the FDA announced it was going to be conducting a series of inspections in an effort to evaluate industry's compliance and understanding of Part 11 in light of the enforcement discretion described in the August 2003 'Part 11, Electronic Records; Electronic Signatures — Scope and Application' guidance. The FDA had firmly laid down its intentions on 21CFR11 compliance and enforcement. **[Source FDA Website]**. Therefore 21CFR11 is a crucial design and functional consideration for EMS software.

With such emphasis on the EMS 21CFR11 design it is worth evaluating the vendors EMS software very carefully and the best approach is through a traceable matrix aligned against the FDA 21CFR11 requirements and the EMS User Requirement Specification (URS). Building a matrix into the design allows for easier validation and testing protocols to be developed and this enables auditors to see how the software meets the requirements. Internal SOPs for some 21CFR11 requirements will need to be developed and put into practice.

What is Validation?

Action of proving, in accordance with the principals of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to expected results, **[Eudralex - Volume 4 GMP Guidelines Glossary]**

“Validation” of computer systems is the process that ensures the formal assessment and reporting of quality and performance measures for all the life-cycles stages of software and system development. Its implementation, qualification and acceptance, operation, modification, requalification, maintenance and retirement. **[PI 011-3 “Good Practices for Computerized Systems in “GXP” Environments” Pharmaceutical Inspection Cooperation Scheme (PIC/s), September 2007]**

In early 2010 there was also a shift of focus on selection of Software and Computerized Systems EUGMP and Annex 11 Computerised Systems came into operation 2011. Therefore following guidelines of this standard are recommended. The actual validation protocols need to be developed and this leads back to the EMS software traceability matrix as a starting and a reference point in the design.

What are the Regulatory Requirements for Software Validation?

For example in Medical device manufacturing. Software validation is a requirement of the Quality System regulation, which was published in the Federal Register on October 7, 1996. Reference Title 21 Code of Federal regulations (CFR) Part 820 and 61 Federal Register (FR) 52602. Unless specifically exempt in a classification regulation, any medical device software product developed after June 1, 1997, regardless of its device class, is subject to applicable design control provisions and must be validated upon installation and if any changes are made post installation.

To summarize the FDA part 11 requirements they are outlined as;

- Promote a “risk based” approach to GMP
- System Validation
- Record Copying
- Record Retention
- Audit Trail
- System Access
- System Security



Fig.2 Validation of remote particle sensor in Cleanroom

What is EUGMP Annex 11 Computerized Systems?

First released in 2011 Annex 11 applies to all forms of computerized systems used as part of a GMP regulated activities Annex 11 is a checklist of non-prescriptive requirements that was adopted by EU GMP to establish the requirements for computerized systems used in the production and distribution of medicinal products

Good Manufacturing Practice (GMP) ensures medicinal products are produced consistently and controlled to the quality standards appropriate for their intended use and as required by product specifications or marketing authorization. Annex 11 details the European Medicines Agency (EMA) GMP requirements for computer systems. Many USA based Manufactures export to Europe and the FDA are part of PICs so Annex 11 Computerized systems requirement is not just isolated to Europe.

What is Risk Mitigation?

With the growing demand for real-time monitoring systems and the need for improved quality process data and reliable environmental monitoring data big Pharma has been focusing on Risk Mitigation.

“Risk Management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product across the product lifecycle.” (ICH Q9 2006)

As well as a formal internal Risk Assessment another critical requirement is to conduct a System Supplier Audit – To reduce risks to the quality of product which is the overall goal of the risk mitigation process for a Pharma company the supplier audit is the critical first step in determining which supplier is the best supplier for their process and product quality. The Audit Plan should cover the following areas as a minimum;

- Quality System
- Quality Management
- Software Development Life-Cycle
- GAMP
- Manufacturing Facility
- Service Support
- Technical Staff

DATA INTEGRITY

Fundamental to a Monitoring Systems design is Data Integrity. This is a crucial factor in GMP manufacturing data reliability, data integrity, data security, is the data validated can the data be manipulated? All these question are very relevant to selection of computerized systems. Data integrity is achievable with a robust data governance approach to ensure all data is complete, consistent and accurate. In March of 2015 the UK’s Medicines and Healthcare Products Regulatory Agency (MHRA) released a Guidance for Data Integrity. This guidance discusses system design, data integrity, data risk and data records with an emphasis on the task being performed, identifying the person(s) performing the task and an appropriate SOP being used as well as the level of validation required for the process.

What do Regulators look for?

- Backdating
- Fabricating data
- Missing data
- Missing comments on alarm acknowledgements
- Sample reruns

- Not recording activities
- Releasing failing product
- Testing into compliance
- Not saving electronic or hard copy data

Design Controls for Data

Quality by Design is the best approach but first you need to apply design controls for your data.

- Identify Critical Data
- Identify risks
- Determine confidence level
- Establish meaningful data reporting
- Establish controls over data lifecycle
- Generate proof (Audit trails, checklists)

In 2016 the Parental Drug Association (PDA) released guidance on a code of conduct for Industry. This guidance was collaboration between the PDA and the FDA and the aim was to ensure rising data integrity lapse problems would be detected and reduced. This code is a voluntary code and not mandatory one. The goals of the code are outlined below.

1. Promote harmonized standards for compliance with regulatory expectations for maintaining data integrity
2. Define mechanisms for detecting non-compliance and outline a clear methodology for remediating gaps
3. Serve both industry and regulators by creating and defining solutions for the increasing number of failed inspections where firms lack not only the necessary controls to ensure data integrity but also the expertise to detect and resolve non-compliance
4. Develop a methodology for restoring confidence in a system and organization to avoid revenue loss and regulatory impacts

What is a Data Integrity Program?

A data integrity program is a significant component of a company's Quality System, providing foundational assurance that the data used to demonstrate a company's products are safe and effective for their intended use are in compliance with regulatory requirements. Below is a summary of such a program outlined by the PDA recently which outlines elements of a code of conduct for data integrity in the Pharmaceutical Industry.

Elements of A Code Of Conduct For Data Integrity

- Applicability
- Data Collection, Analysis, Reporting and Retention
- Electronic Data Acquisition Systems
- Electronic Access Security Measures
- Auditing of Quality System for Data Integrity

- Investigations of Wrongful Acts
- Reporting Wrongful Acts
- Disciplinary Actions for Employees due to Wrongful Acts
- Notifying Regulatory Authorities about Data Integrity Issues
- Data Integrity of Outsourced Services & Purchased Raw Materials
- Employee Training

MONITORING SYSTEM DESIGN AND IMPLEMENTATION

How do you design all of these elements into a Monitoring System suitable for Your Needs?

Let's look at a few crucial factors to consider Monitoring System capabilities.

- Must be GAMP designed and developed
- Must generate a URS from a formal Risk Assessment
- Must meet 21CFR11 requirements with assistance of SOPs
- Must meet EUGMP Annex 11 requirements
- Must have data integrity
- Must be validated
- Must have traceability back to the URS
- Must have a Service Level Agreement

Below is a step by step Matrix to help guide you in the planning and design of an Environmental Monitoring System (EMS) from start to finish with responsibilities outlined between Customer and Supplier.

EMS PROCESS FLOW – EMS Design and Implementation			
		Short Description	Responsible
Risk Assessment	Develop Risk Assessment	A formal risk assessment is developed based on the guidelines of EUGMP Annex 20 or ICHQ9	CUSTOMER
URS	Develop URS	A URS is developed by all Company stakeholders, the URS outlines the EMS requirements based on the findings of the Risk Assessment	CUSTOMER
Quote	Submit Quote	The EMS Supplier develops a Quote based on the URS	EMS SUPPLIER
Audit EMS Supplier	Supplier Audit	Customer conducts site audit of EMS Supplier QMS and Software development process and service support (EUGMP Annex 11 Computerized Systems)	CUSTOMER

Select EMS Supplier	Select EMS Supplier	Based on Risk Assessment the Customer selects a Primary EMS supplier with a secondary backup supplier once a P.O. is provided the project commences.	CUSTOMER
Start of System Project Management	Kick Off Meeting	The kick Off Project Management meeting is critical to confirm the project schedule, introduce the key Managers and set the objectives and goals of the project. A Gantt Chart is typically used by the Project Manager to Schedule and track the project. Good communication is critical throughout the project and weekly project meetings Keep the project on track as well as daily site updates.	CUSTOMER EMS SUPPLIER
EMS Quality Plan	Quality Plan	The quality plan is a document, that specifies quality standards, practices, resources, specifications, and the sequence of activities relevant to a particular product, service, project, or contract. The Customer must review and sign off the Quality Plan.	EMS SUPPLIER
Functional Design Specification	FDS	A Functional Design Specification (FDS) is a document used by companies in a pre-development phase to translate all notes, concepts, and scope into a complete requirements document. The document can include anything from flowcharts, screenshots, and wiring diagrams to describe the functionality of the system. It is always best practice to develop the FDS using the URS as the main driver. The Customer must review and sign off the FDS.	EMS SUPPLIER

Design Review	Design Review	The design review is a milestone within a product development process whereby a design is evaluated against its requirements in order to verify the outcomes of previous activities and identify issues before committing to - and if need to be reprioritized further work. The ultimate design review, if successful, therefore triggers the system build.	CUSTOMER EMS SUPPLIER
System Build and Test	Build & Test	The Build and test stage of the EMS lifecycle is where The EMS software is configured and the hardware is connect. Once connected the system is tested for functionality and connectivity. After build and test is completed the system is then ready for a formal FAT.	EMS SUPPLIER
Factory Acceptance Test	FAT	The factory acceptance test (FAT) is a test conducted at the EMS suppliers premises to verify that the system operates accordingly to the specifications of the FDS. The Customer must review and sign off the FAT.	CUSTOMER EMS SUPPLIER
System Delivery	System Delivery	After successful FAT the system is securely packaged and shipped to site.	EMS SUPPLIER
Site Acceptance Test	SAT	A formal site acceptance test occurs once the system is unpacked to verify connectivity and functionality on-site. The SAT is typically completed so the system is ready for and IQ/OQ The Customer must review and sign off the SAT	CUSTOMER EMS SUPPLIER
Installation Qualification	IQ	tested during the site acceptance testing. A successful SAT paves the way for a successful IQ. The IQ should be traced back to the URS. Meaning the protocol IQ tests should indicate the critical attributes in the URS have been formally tested in the IQ The Customer must review and sign off the IQ and witness the testing	CUSTOMER EMS SUPPLIER
Operation Qualification	OQ	The OQ is completed after the IQ has been signed off. The OQ should be traced back to the URS. Meaning the protocol OQ tests should indicate the critical attributes in the URS have been formally tested in the OQ and the system proves operational functionality. It is recommended a 24-48hr dry run is performed to validate the Monitoring system can run without any issues prior to handover The Customer must review and sign off the IQ and witness the testing	CUSTOMER EMS SUPPLIER
System Training	Training	Sufficient training needs to be provided and this is a critical step in the handover process. Training needs to be measurable and the operator and/or administrator needs to show repeatability. The training should have a formal exam based on witnessed and successful end user performances. The training provided should be well developed so the end user can perform their PQ without vendor assistance	EMS SUPPLIER
Performance Qualification	PQ	The Customer should perform a live PQ once the monitoring system has been handed over. This PQ should be based on a live process run and scenario. It is at this stage that final configurations and any alarm adjustments are made and captured with Change Control. SOPs should be executed and well understood especially with 21CFR11 requirements and what the procedure is when an Alert or Action Alarm is triggered. Any intuitive Auditor will look for these SOPs in place and been used	CUSTOMER

IN SUMMARY

With the ever changing GMP and Regulatory compliance requirements and the standards in place and the fact that a Cleanroom continuous Environment Monitoring System is a fundamental process tool to monitor the manufacturing environment. It is critical that the planning, design, procurement, implementation, validation, performance and ongoing maintenance are meticulously organized. This article is designed to help and assist those of you who are in a position of Quality, technical and Production Management in a Life-Science manufacturing environment. The information here comes from many years on hands experience in this Industry.

The importance of incorporating such a strategy as outlined above will save issues that may arise further down the track of such a Project. A risk assessment designed URS is a major contribution to a successful Monitoring System and a well-developed testing and validation process is crucial. Selecting the right vendor with the ability to offer this type of experience is critical to the success of a Project and a vendor audit is a positive move at the start of the process to ensure you are working with the right supplier.

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