LIGHTHOUSE
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CREATING A COMPLIANT ENVIRONMENTAL MONITORING PROGRAM

Lighthouse Worldwide Solutions

Overview

There are a number of both governmental and private industry recommendations and regulations surrounding product quality in the pharmaceutical industry. Over the years, they have evolved to meet the modern demands of the industry, such as data integrity in the digital age. This paper outlines the basic definitions of some of the guidelines and regulations, as well as the importance of choosing an EMS vendor who will help you meet these requirements.

Improving Quality Through Compliance

The pharmaceutical industry is always looking for ways to improve quality. One of the ways quality is monitored during production is through GMP and 21CFR11 in the context of GAMP5. That is why it is important you stay up to date on these guidelines and regulations.

How a company creates, maintains, retrieves, corrects, and controls data can affect product quality. Moreover, their reaction to out of tolerance conditions via continuous Environmental Monitoring Systems (EMS) alarm notification is crucial to the process operation and the product quality. Thus, the EMS becomes a critical process tool to ensure product quality and the data itself.

As far as electronic records are concerned, the FDA's main focus has stayed the same since the introduction of 21CFR11. That is "to safeguard record integrity in order to ensure product quality". Therefore "record integrity and data integrity" is a focused on during regulatory audits. It makes sense to have a robust EMS that can be validated to confirm it meets the requirements of regulatory compliance. This means that pharmaceutical manufacturing companies should be looking closely at their vendors for support in continuous quality improvements.

In recent years, pharmaceutical companies have been utilizing risk mitigation as a selection tool for the correct EMS provider. The emphasis has been on strong validation support, ongoing technical support, down time reduction, and over all production loss reduction. While it might not be apparent, these reasons show that choosing the wrong vendor can impact business continuity.

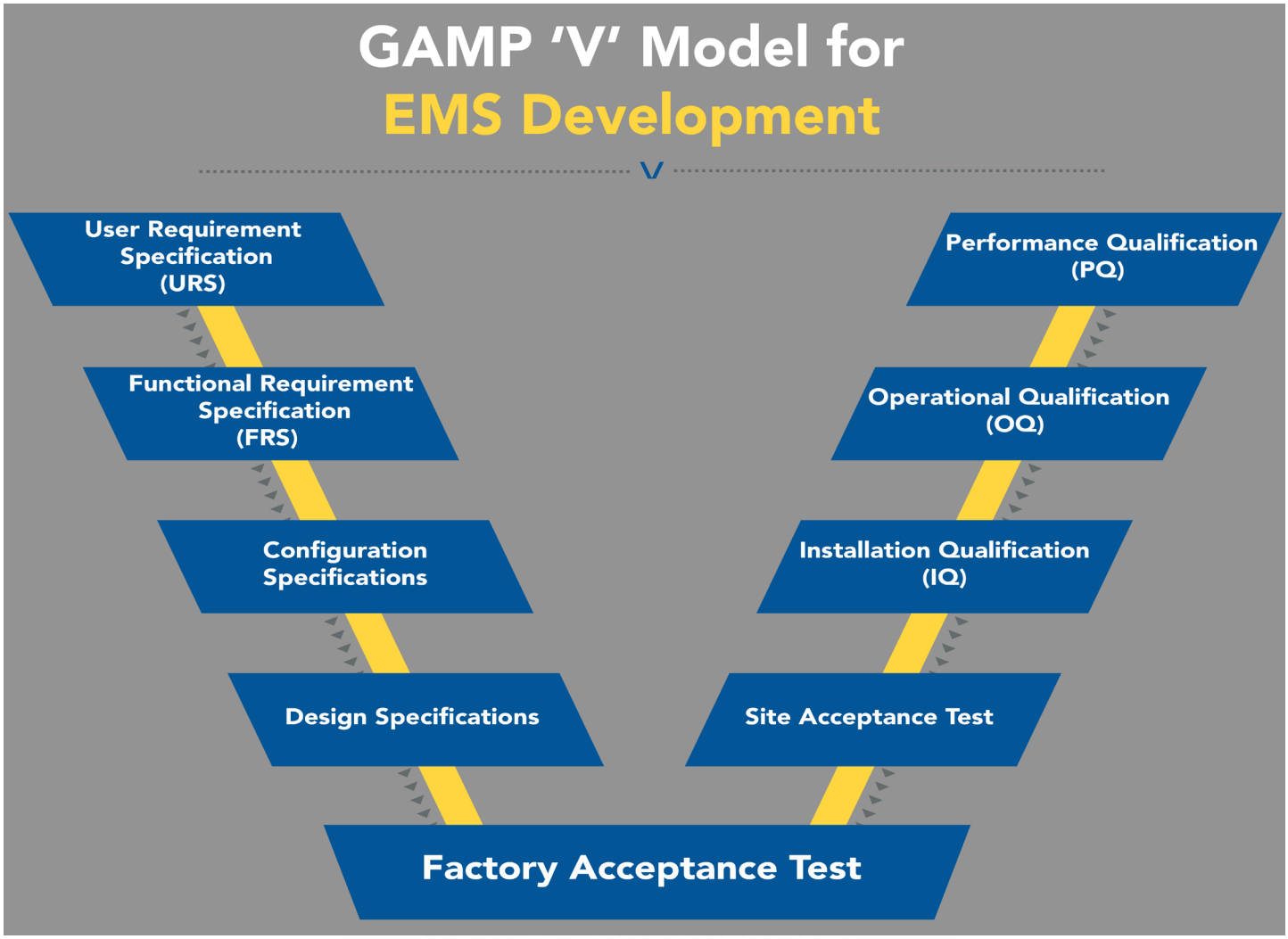
Your vendor should have an excellent grasp on GMP, GAMP, and 21CFR11 requirements – and be willing to work with you in the coming years to verify product quality.

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.

What is 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. 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.



What is 21CFR11?

What is commonly referred to as 21CFR11 is actually the 11th 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 sometimes called, defines the criteria under which electronic records and electronic signatures are considered trustworthy, reliable, and equivalent to paper records.

When 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. Seven years later, 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 it intentions on 21CFR11 compliance and enforcement; therefore, 21CFR11 is a crucial design and functional consideration for EMS software.

With such emphasis on the EMS design, it is worth evaluating the vendors EMS software very carefully. 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. This enables auditors to see how the software meets the requirements. Internal SOPs for some 21CFR11 requirements are needed.

What is Validation?

Validation is the action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity, or system actually leads to expected results.

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. You will look at the implementation, qualification and acceptance, operation, modification, requalification, maintenance, and retirement.

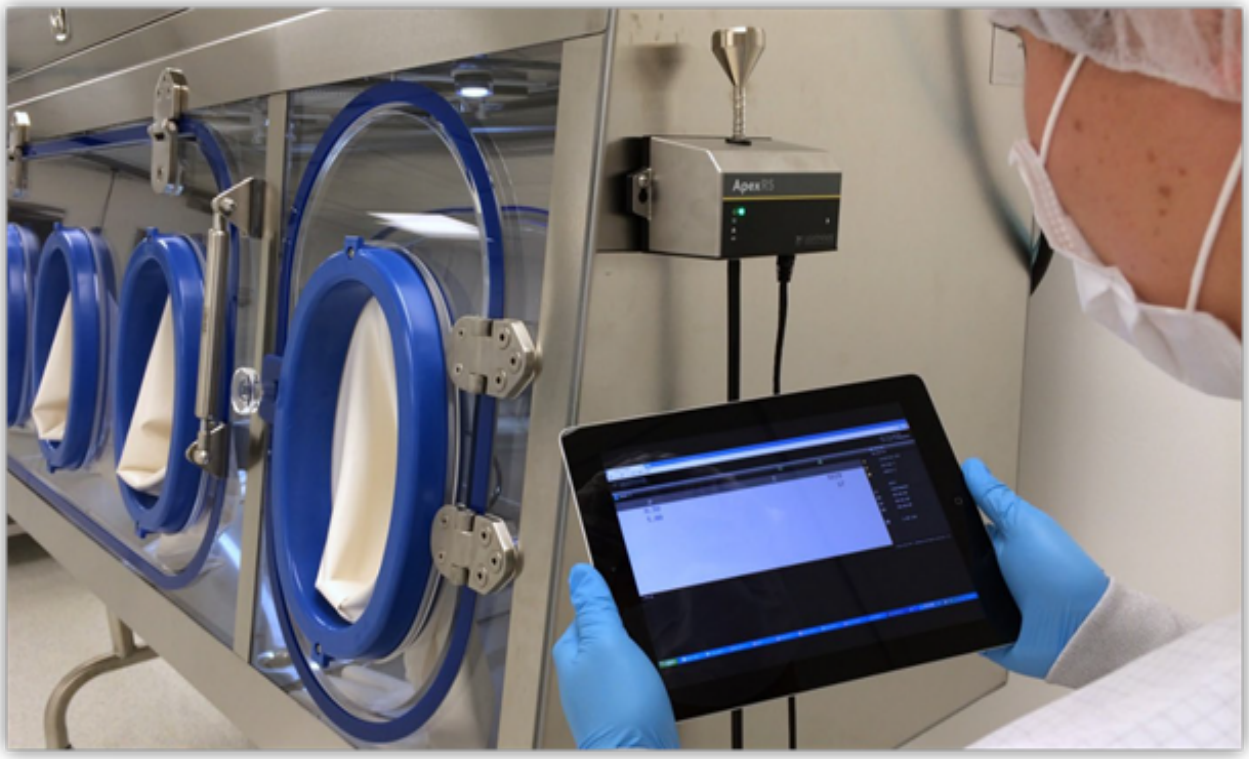
In early 2010, there was also a shift of focus on selection of software and computerized systems. EUGMP (the European Union version of GMP) and Annex 11 Computerized Systems came into operation 2011. Therefore, it is recommended to follow the guidelines of these standards.

Proper validation protocols require development, which leads back to the EMS software's traceability matric. This is an excellent starting and reference point in the design.

What Are The Regulatory Requirements for Software Validation?

The regulatory requirements for software validation depends on your industry. 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. You can 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**



What is EUGMP Annex 11 Computerized Systems?

Annex 11 was first released in 2011. It 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 EUGMP 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 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, the pharmaceutical industry 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, you should also conduct a System Supplier Audit. This reduces risks to the quality of product, which is the overall goal of the risk mitigation process for a pharmaceutical company. The Supplier Audit is the critical first step in determining which supplier is the best option 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

In audits and in your SOPs, you will need to address questions such as: Is the data validated? Can it be manipulated? These are answered by how confident you are in your data integrity, which starts with your EMS and other computerized systems.

Data integrity is the cornerstone of an EMS because it is fundamental to GMP data reliability and security. 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 acknowledgments**
- **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 for determining the quality in the final product. 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 the pharmaceutical Industry. This guidance was a collaboration between the PDA and the FDA. The aim was to ensure rising data integrity lapse problems would be detected and reduced. This code is a voluntary code and not a mandatory one. The goals of the code are:

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 dictates 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?

An excellent EMS:

- **Must be GAMP designed and developed**
- **Must generate a URS from a formal Risk Assessment**
- **Must meet 21CFR11 requirements with the 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**

In Summary

GMP, GAMP5, and 21CFR11 in relation to GAMP5 all provide critical, but constantly evolving, compliance guidelines and requirements to product the quality of the end product. An Environmental Monitoring System (EMS) is the cornerstone of fulfilling these requirements and ensuring data integrity.

It is critical that the planning, design, procurement, implementation, validation, performance and ongoing maintenance are meticulously organized. The information we have presented 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.

Visit our Knowledge Center for more information on Cleanroom Technology and its applications.

https://www.golighthouse.com/en/knowledge-center

References:

- *FDA – Sterile Drug Products produced by Aseptic Processing – Current Good Manufacturing Practice (2004).*
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- *PI 011-3 Good Practices for Computerized Systems in GXP" Environments [Pharmaceutical Inspection Cooperation Scheme (PIC/s), 2007]*
- *GAMP 5 (2008)*
- *ISO 14644-1 Cleanrooms and associated controlled environments – Part 1 Classification of air cleanliness (1999)*
- *ISO 14644-1 Cleanrooms and associated controlled environments – Part 1 Classification of air cleanliness (2015)*
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- *The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems, GAMP 4 (2001)*
- *ISO 14971:2002 Medical Devices- Application of risk management to medical devices (2001)*
- *Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach; A Science and Risk- Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach (FDA 2002)*