Meeting Compliance to Electronic Record and Electronic Signature Requirements: The Risk-based Approach

Life sciences companies that choose to maintain electronic records to meet predicate rules including Good Practices (GxP) and Current Good Manufacturing Practices (cGMP) are required to validate their electronic record-keeping systems. This is to ensure accuracy, reliability, and consistent intended performance of the system and to determine invalid or altered records.

The United States Food and Drug Administration (FDA) and the European Union (EU) have issued regulations that provide criteria for the acceptance of electronic records and signatures equivalent to paper records and handwritten signatures.

The objective of this white paper is to describe the risk-based approach and stepwise process for meeting the electronic record and signature compliance criteria.
About the Author

Nandan Thakur

Nandan Thakur is a Regulatory IT Compliance Consultant with the Pharma IT Solutions and Innovation Group of the Life Sciences Industry Solution Unit (ISU). He has been associated with TCS for almost four years. Nandan has 18 years of relevant experience and is actively involved in IT compliance activities such as Computer System Validation and Electronic Record/Electronic Signature (ER/ES) regulations for Life Sciences customers.
# Table of Contents

1. Introduction ........................................... 4
   1.1 An Overview and Application of Electronic Records and Signature Compliance Regulations ........... 4

2. Risk-based Approach for Electronic Records and Signature Compliance ........................................ 5

3. Conclusion .............................................. 8

4. Acknowledgements ....................................... 8

5. References ............................................. 8
Introduction

The life sciences industry faces challenges such as increasingly stringent regulations that require heavy documentation. In the past, there were traditional methods of documentation including paper records with handwritten signatures and filing of papers in storage units. However, with the growing focus on regulations along with advancements in technology, electronic records have become imperative. With paper records being gradually replaced by electronic records and handwritten signatures by electronic signatures, there has emerged the need for ensuring that the electronic records and electronic signatures are considered as reliable as the earlier forms.

Life sciences companies have approached regulatory bodies for approval to use electronic records and signatures instead of paper records and handwritten signatures.

For organizations to be able to prove that their records were trustworthy and reliable, the US FDA in 1997 introduced a rule for the usage of electronic records and signatures in life sciences companies. This rule, 21 CFR Part 11, was further reviewed and led to a new guidance promoting a narrower scope, in September 2003. On January 3, 2011, the European Commission published a new Annex 11: Computerized Systems as part of The Rules Governing Medicinal Products in the European Union Volume 4 GMP.

These regulations regarding the use of electronic records and signatures are part of the FDA and EU’s efforts to set minimum compliance guidelines for computerized systems operating in the pharmaceutical industry.

An Overview and Application of Electronic Record and Signature Compliance Regulations

Electronic record and signature compliance regulations establish requirements to ensure that electronic records and electronic signatures are trustworthy, reliable and equivalent substitutes for paper records and traditional handwritten signatures.

Part 11 establishes the technical and procedural control guidelines that must be met by the GxP IT systems used to maintain regulated records electronically.

European Union (EU) Annex 11 covers the interpretation of the principles and guidelines of GMP-regulated activities to computer systems. It applies to the GMP for medicinal products and investigational medicinal products meant for human use, and veterinary medicinal products.

These regulations have been set to ensure that computerized systems used in the GxP environment for controlling the processes and managing regulatory data have no adverse impact on product quality, product efficacy, or patient safety. The systems must demonstrate the integrity, confidentiality, authenticity, accuracy and availability of the regulatory electronic data.

The electronic record and signature regulations apply to any electronic record governed by an existing predicate rule that is created, modified, archived, retrieved, or transmitted using computers and/or saved on durable storage media. The regulations apply to records required by what the FDA refers to as a predicate rule. A predicate rule is a previously published regulation, collectively known as GxP such as Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP).
The predicate rule mandates:
- What records must be maintained
- The content of records
- Whether signatures are required
- How long records must be maintained

Under the narrow scope, Part 11 / Annex 11 applies to:
- Electronic records that are maintained in lieu of paper records and are to be maintained to meet the requirements of FDA Predicate Rules or records created and maintained as part of GxP.
- Electronic records submitted to the regulatory bodies.

Part 11 / Annex 11 will not apply when computers are used to generate paper printouts of electronic records if:
- These paper records meet all predicate rule requirements and
- The department relies only on the paper records to perform regulated activities

Electronic record and signature compliance regulations highlight the exercise of ‘enforcement discretion’ for the requirements. These requirements relate to:
- Validation
- Audit trails
- Legacy systems
- Data archival and retrieval
- Copies of records
- Record retention

All GxP IT systems creating and managing regulatory records require validation and sufficient audit trails to ensure compliance. Further record retention policies must be maintained to account for the legal defensibility of all electronic records in question.

**Risk-based Approach to Electronic Record and Signature Compliance**

With the ER/ES regulations being in place, it is imperative that the systems that are managing electronic records and/or electronic signatures are compliant with the 21 CFR Part 11 and EU GMP Annex 11 regulations. It has been easy to deploy the requirements of 21 CFR Part 11 / Annex 11 for new systems as part of the development and deployment. However, it has been a challenge to address the electronic record-signature requirements for legacy systems already in use that have either not been assessed or have been previously assessed against then-existing requirements.

To address this issue, a three-stage risk-based process for incremental or total validation or testing is recommended, encompassing the entire electronic record and signature compliance process. This approach comprehensively defines a method to implement the processes to provide a high degree of assurance that the system, in all its facets (processes, people, and systems), will perform as per its intended requirements, adhering to electronic record and electronic signature compliance guidelines.
This process consists of three stages -
1) Plan - Preparation and Planning
2) Assess – System Assessment and Gap Analysis
3) Execute - Remediation Plan and Plan Implementation

**Plan - Preparation and Planning**

As a first step in achieving the ER/ES requirements, the validation team, along with the client and subject matter expert, performs a review of the company approach and policies for regulatory IT compliance including quality guidelines. An inventory review is performed and a portfolio analysis is conducted to understand the current compliance status and then engage in the planning process.

The steps include:
- Understanding the applicable ER/ES requirements and defining the objectives
- Defining the risk-based approach
- Reviewing the existing inventory list of the systems used in the GxP environment
- Conducting the ER/ES awareness program for those involved, including training on the checklists for regulatory scope determination, regulatory detail assessment, and Part11/Annex 11 assessments
- Understanding the resource requirements with roles and responsibility
- Preparing the activity plan with deliverables

**Assess - System Assessment and Gap Analysis**

The system assessment is performed based on the inventory review and a portfolio analysis of the existing information technology setup. This procedure helps determine whether the application needs to comply with electronic record and signature requirements. The system assessment is performed as the first step to determine the applicable regulations and subsequently, the risk level of the application. A detailed analysis is performed to determine the various kinds of records that are under consideration and their impact on the product attributes of safety, purity and quality. A justification is given on whether the system needs to be made compliant to ER/ES requirements. For systems where it is agreed that they will be validated in order to be compliant to electronic record and signature requirements, a detailed gap analysis will be performed to identify the gaps and the necessary steps to close them.

The key considerations for gap analysis are:
- Hardware (HW)/software (SW) inventory
- Validation status and validation deliverables
- Compliance controls for closed and open systems
- Organizational chart and job descriptions
- Standard Operating Procedures (validation, security, backup/recovery, change control, HW/SW maintenance, operations, training)
- Quality Assurance audits and inspections of computer systems
- Supplier or service provider audits
- IT Infrastructure qualifications
- Change control / Periodic review process
- Training compliance

The outcome of the analysis is a gap assessment report that details the various gaps identified in the portfolio.

A risk-based approach can be adopted to ensure compliance with ER/ES requirements. The steps that are followed include:

- Identifying and defining GxP electronic records and signatures, based on the predicate rules, criticality of the process and risk to product safety, efficacy, and quality
- Assessing the impact and risk of electronic records. In addition to the requirements from predicate rules, an assessment is performed with respect to impact on and hazards to patient safety or product quality on a scale with ratings such as High Impact, Medium Impact and Low Impact
- Implementing controls commensurate with the criticality of the electronic record and risks or hazards identified for that record. These controls are documented and justified by mapping them to the identified risks
- Validating implemented controls and critical functionalities

This approach focuses on the critical records compared to all electronic records created by a firm and allows the life sciences industry to analyze the existing business process, identify GxP critical records, and deploy technical or procedural controls to mitigate risks. This is demonstrated in the figure below.
Execute - Remediation Plan and Plan Implementation

After the completion of the gap assessment, a plan is created to address the identified gaps along with timelines. Based on the identified regulations and risks, an approach is adopted to validate the applications and achieve compliance to ER/ES requirements.

The various applications and business processes are prioritized based on business criticality, data integrity and complexity. The plan will include –

- Detailed activities to be performed for each system
- List of deliverables
- Timelines for achieving the compliance state of the system
- Project plan and resource management
- Roles and responsibilities of the project team
- Requirements for modifying the process and modifying the system design
- Technical or procedure controls for managing the hazards, training compliance requirements etc.
- Procedural and technical controls including security management, backup and restore with disaster recovery, business continuity plans, audit trails, change control for software and hardware, policies and procedures for quality processes, management of hybrid records and the maintenance of compliance status.

The plan is implemented in phases with differing degrees of rigor based on the impact of records and risks identified.

Conclusion

The risk-based approach to electronic record and signature compliance is both comprehensive and flexible, enabling any organization to address compliance and validation requirements of ER/ES guidelines in an effective manner, irrespective of the size and nature of technology. This approach helps the organization to:

- Transform systems, processes and stakeholders into a state of constant compliance/validation in a cost-effective manner
- Automatically ensure compliance when implementing process and technology innovations
- Manage systems and processes to meet compliance requirements throughout their lifecycles

Acknowledgements

I would like to thank Sanjeev Sachdeva, Head of Pharma Innovations and Solutions, for his guidance and support, and for being a continuous source of motivation while writing this white paper. I would also like to thank group team member Kavitha AyalaSowmayajula for her support and review.

References
