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Review Article

**Introduction to 21 CFR 11 - Good Electronic Records
Management**

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West Bengal, India.**ABSTRACT**

Pharmaceutical stake holders such as drugs manufacturers, medical device manufacturers, biotechnology companies and biologics developers regulated by the FDA need to be aware of the requirements for CFR 21 Part 11 compliance. Part 11 was developed in response to the soaring costs associated with managing the distribution, storage, and retrieval of paper records used in conjunction with the FDA. Further, FDA-regulated companies are very familiar with a variety of validation processes ranging from full process and facilities validation to that of qualifying individual utilities, equipment, instruments and everything in between. When it comes to 21 CFR Part 11 and computer systems validation, the use of vendor-supplied "off-the-shelf" configurable software offers many challenges to validation, including supplier audits. FDA's interpretation of 21 CFR Part 11 for inspections of computer systems and computer validation has been refocused through the Scope and Application Guidance to emphasize predicate regulation record requirements and shift the emphasis to documented risk assessment. Compliance will remain a part of routine FDA inspections based on predicate regulations, including validation. FDA insists that Software and Computer System Life Cycle principles in a GxP setting should be supported by a Corporate Computer Systems Validation Policy with supporting global SOPs for the System Development Life Cycle, Validation, Supplier Assessment and Audits, Change Control, and Revalidation along with local SOPs for specific systems containing strict guidelines with concept, user and functional requirements and design phases, followed by the implementation and testing with qualification protocols.

Keywords: FDA, 21 CFR 11, GAMP, Predicate Rule, Electronic signature.

INTRODUCTION

In today's world, Records - whether it is a document, an e-mail, instant message or a transaction - can prove innocence or lack of intent. In the event of a dispute, Good electronic records management practices offset what could be considerable costs for legal discovery and audits by making relevant business records readily available. The difference could be millions of dollars.

Customized Integrated Computer system are more and more widely used during the phases of development, Clinical Trial, automated manufacturing and testing of drugs and medical devices for generating data & records, which should be available, traceable & auditable for inspection to Regulatory authorities like FDA. Proper functioning and performance of software and integrated computer systems play a major role in obtaining consistency, reliability and accuracy of data. Therefore, computer system validation (CSV)

should be part of any good development and automated manufacturing practice (GAMP).

OBJECTIVES

Presently, the FDA actively encourages that all New Drug Applications (NDA's) and equivalent license applications for medical devices and biologics be submitted to the agency in electronic form. Given this mandate, the need for compliance to 21 CFR Part 11 will only intensify. 21 CFR Part 11 was developed initially as a response by the FDA to allow Life Science Organization's use of electronic signatures in electronic batch records. It is applicable to records identified in predicate rules, such as Good Clinical Practices (GCP), Good Laboratory Practices (GLP), and Good Manufacturing Practices (GMP). The purpose of the regulations is to ensure both the accuracy and trustworthiness of information and data as it is handled and traced to establish the reliability of

data submitted to the agency for drug or device approval process.

Title 21 in the *Code of Federal Regulations* regulates the Food and Drugs in United States of America. **Part 11** within this *Code of Federal Regulations* is related to FDA guidelines about electronic records and electronic signatures. The regulations in this part set forth the criteria under which the FDA considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper. 21 CFR Part 11, states the requirements for procedures for creating, modifying, maintaining, archiving, retrieving, and transmitting electronic records and electronic signatures (Biometric signatures preferable) by virtue of which they can be considered or rendered to be trustworthy, reliable and equivalent to paper records. CFR 21 Part 11 requires that a drug manufacturer, medical device manufacturer and biologics developers and all other industries regulated by FDA to implement controls for their electronic system, like audits, documentation for software, system validations, audit trails, electronic signatures – both Digital & Biometric, and for systems which are handling the electronic data which is required to be maintained by the FDA predicate rules or the systems which process data used for demonstration of compliance of a requirement or a rule.

- In Laboratory situations, this includes any laboratory results used to determine quality, safety, strength, efficacy or purity (GLP).
- In Clinical trials, this includes all data to be reported as part of the clinical research used to determine the safety, toxicity, efficacy of the trial (GCP).
- In manufacturing environments, this includes all decisions related to product release and product quality (GAMP, GXP & cGMP).
- CFR21 part 11 also applies to the electronic submissions made to FDA like ANDA, NDA.

Paper documents are still considered if a firm keeps "**Hard copies**" of all mandatory records; for regulatory purpose the paper documents are also considered as authoritative documents. Records must also be maintained or submitted in accordance with all predicate rule requirements, including predicate rule record and recordkeeping requirements. If electronic records are illegible, inaccessible, or corrupted the manufacturers are still subject to those requirements.

THE SALIENT REQUIREMENTS OF 21 CFR 11

- Validation
- Limited access to systems and data

- Control of system documentation, security & archiving.
- Accurate & raw data generation & protection of data integrity
- Electronic audit trail
- Requirements related to electronic signatures & binding signatures with records- handwritten, electronic (Biometric)
- Digital signatures for open systems
- Accountability for electronic signatures
- Accountability of maintaining authentic records
- Accurate and complete copies
- Instant retrieval of data and meta data for FDA access
- Use of operational system checks, Use of authority checks, Use of device checks
- Training/qualification of people & establishment of written policies of responsibility.

The computerized records that the firm keeps to make it easier to sort or find certain information would not necessarily have to comply with Part 11 regulations. According to the old interpretation the mere existence of electronic data in or around a product or plant was considered to be an electronic record of the rule. For example: If a firm has a database for product complaints history and follow up, but still records everything on paper (**and the printed paper copy is the official record**), the database would not have to comply with Part 11. **However, if the database is the only record, the database would have to comply with Part 11.**

Data integrity and fraud -another looming crisis

However, security concerns surrounding wet ink signatures surfaced as it became apparent these signatures including the content they were attesting to could be easily falsified. There had been incidences reported that loss of data integrity, data manipulation and fraud appears to be increasing. Regulatory agencies have also noted that analytical laboratories are using electronic record system for processing and storage of data from precision analytical equipments like the Atomic absorption and HPLC instruments,

- Equipments are not set up to control the security and data integrity in that the system is not password controlled,
- There is no systematic back-up provision, and no trace of audit trail of the system capabilities.
- The system does not appear to be designed and controlled in compliance with the requirements of 21 CFR, Part 11, Electronic Records.
- Biased manipulation of data resulting in the acceptance of failed runs

- Intentional manipulations of chromatograms by cutting & pasting chromatographic data so that initial out-of-specification test results are brought into specifications
- Altering weights of samples and standards in analytical calculations
- Changing chromatogram processing parameters
- Manipulation of operation parameters of stability testing data changing calculations to bring out-of-specification results within specifications
- Placed the in-specification assay results into the batch production and control record
- In order to overcome the issues, changes have been brought down for implementing narrowing the scope of 21 CFR 11.
- Risk based validation, record retention, electronic copies, e-audit trail
- Extend risk based controls to other areas of Part 11
- Enforcement discretion replaced by risk based approaches
- Less prescriptive, e.g., other options for audit trail
- No distinction between closed and open systems

- Can you show me the documents and results of the validation activities?
- Does the validation include: “Pass/fail, signature, date/time stamp”; and “objective evidence - screen prints or page printouts with a link to the direction that generated the output.”?

Verification answers the question: “Was the product built right?”
 and Validation answers the question: “Was the right product built right?”

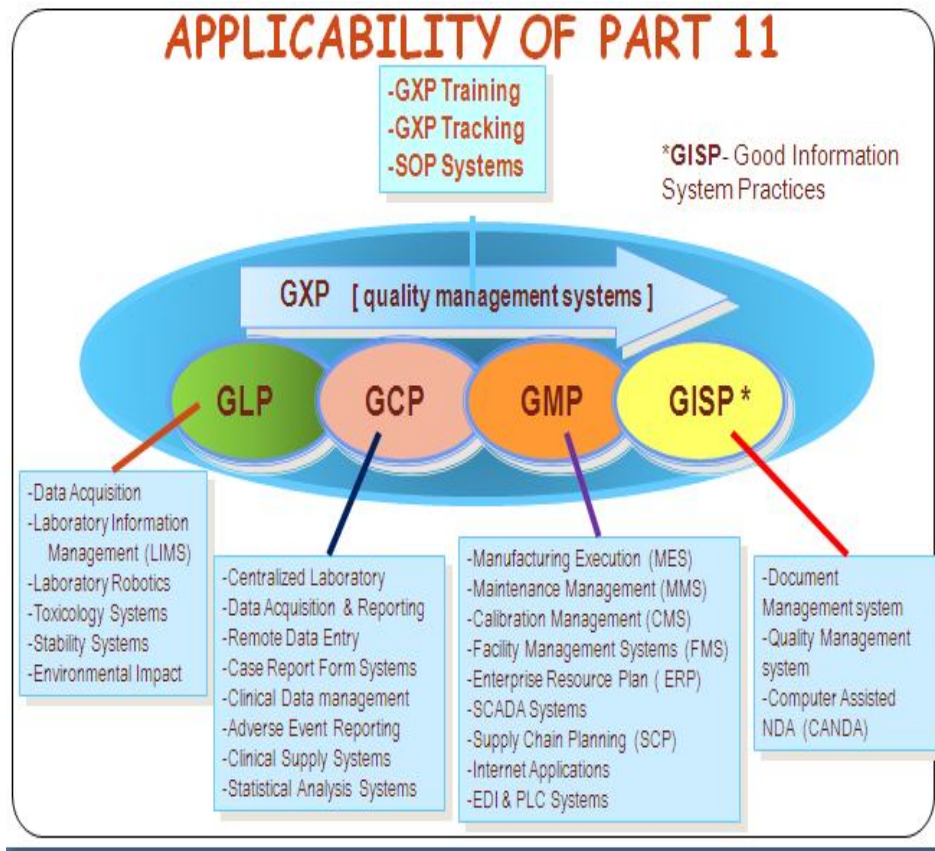
Paper Records / Handwritten Sigs	E-Records / E-Signatures
(+) Fixed Representation (+) Durable (+) Changes Very Evident (+) Copies Evident (+) Signatures Hard to Forge (-) Need Storage Space (-) Inefficiency of Search / Sharing	(+) Global Sharing (+) Rapid Analysis and Search (+) Efficient Review and Approval (-) Changes / Copies Not Evident (-) Selective Data Views (-) Higher Possibility of Data Loss (-) Easy to Forge Signatures

FDA 21CFR11 INSPECTION: FREQUENTLY ASKED QUESTIONS

- Who is allowed to input data?
- Who can access data?
- Who is allowed to change or modify data?
- What is the “Likelihood” for a change of data?
- Can a change impact product quality?
- How do you know who entered and modified the data?
- How do you know which data had been changed?
- When do you lock down the data input?
- Can you do the following actions? - “Show me some data, show me you can see the history of the data, show me you control the data life cycle.”
- Is the system validated and are the requirements met?
- Can you demonstrate compliance with predicate rules without e-records?
- Will the print-outs preserve content and meaning?
- Do regulated activities rely on electronic records?

CRITICAL SUCCESS FACTORS

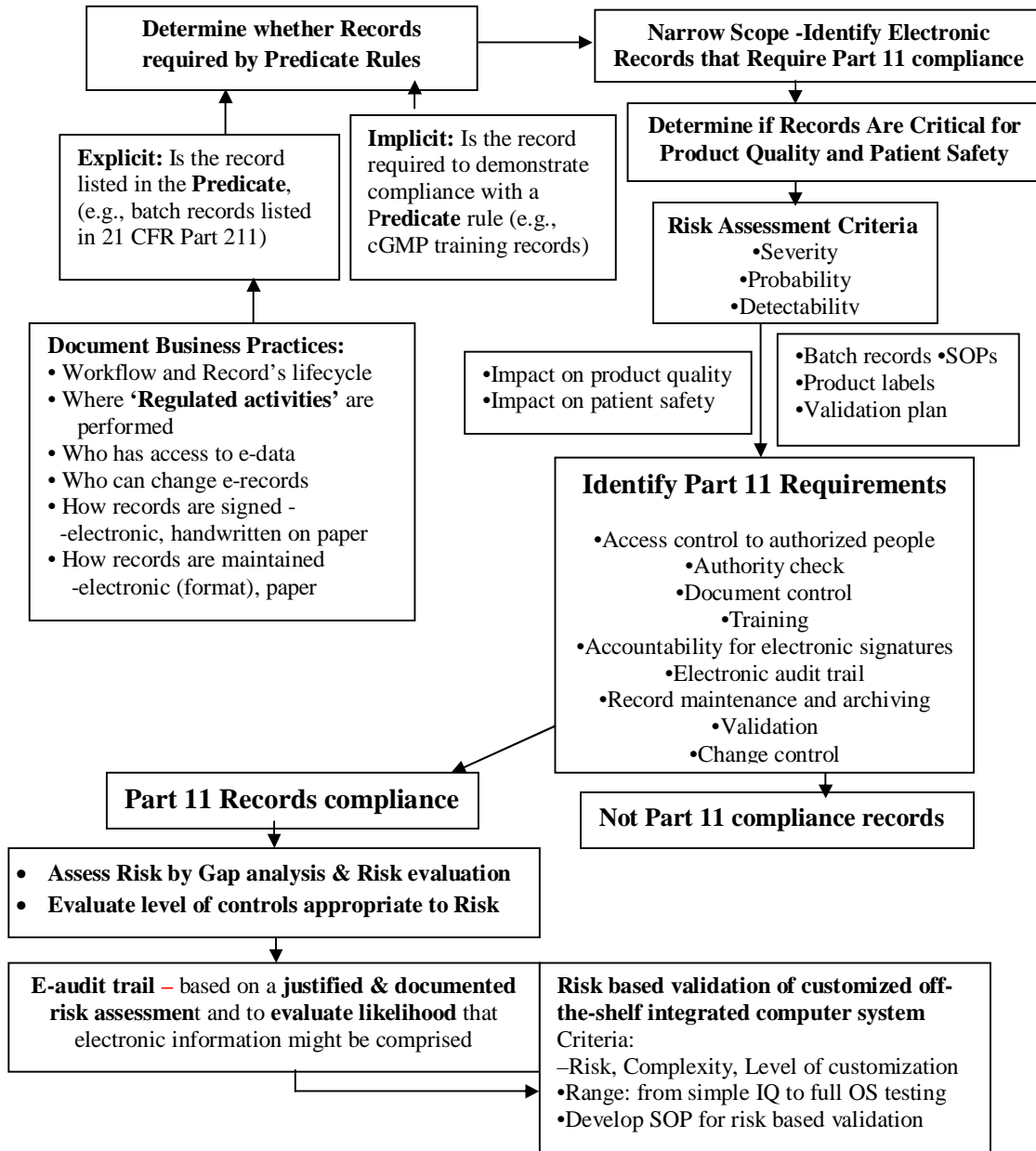
- Validation activities in manufacturing, toxicology, clinical, regulatory and marketing (label approval) will need to be better process focused, requiring definition of inputs and outputs with, procedural controls governing the process activities and standards dictating the format and content of inputs and outputs and well documented.
- Configuration management, security management and periodic review and quality management must be a continual process.
- Record retention and record disposal practices need to be revised to reflect company requirements to comply with new regulatory requirements
- Documentation standards and practices should be created that systematize the processes for creating and maintaining documents.
- Planning will have to take into consideration re-engineering, replacement, or retirement of a computer system when operating costs increase or business process changes.
- Requires effective change control.



<p><u>Advantages</u></p> <ul style="list-style-type: none"> Electronic Batch records can eliminate mountains of paper work, speed processing and allow for statistical and trend analyses. NDA's and other submissions can be submitted electronically in place of paper submission. Increases the speed of information exchange. Cost savings from reduced need for storage space. Manufacturing process streamlining. Job creation in industries involved in electronic record and electronic signature technologies. 	<p><u>Challenges</u></p> <ul style="list-style-type: none"> Firms planning on using electronic signatures in FDA regulated environments will be required to validate the computer related systems. Design of systems must be well thought out and tested thoroughly. Critical control points must be identified which can be monitored through electronic audit trails. Adequate testing of security. Fraud Detection
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STEPS FOR IMPLEMENTATION OF THE NEW APPROACH

1. Identify records required by regulations
2. Identify risks of records-e.g., high, medium, low
3. Document business practices
4. Identify Part 11 requirements
5. Define system requirements
6. Develop and implement project plans



DISCUSSION

In today's complex business environment every company faces regulatory and business mandates of increasing magnitude and frequency that come at an increasingly higher cost. As a result, every enterprise needs to adapt - moving from a compliance-only, departmental, or ad hoc approach to a more enterprise-wide approach to implement 21 CFR Parts 11, as it will affect not only the risk of non-compliance - it affects their bottom lines. While the use of electronic records and signatures brings with it a range of compliance challenges, it will also help to assess and realize tremendous improvements in business process flows, increased data integrity, faster regulatory response, quicker

time-to-market, and increased data security. Inherent in 21 CFR Part 11 compliance is validation of the system used within its current operating environment. However, everyone must still comply with all applicable predicate rule requirements for validation. A Critical approach may be recommended based on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety and record integrity through extensive education and training programs on software/system development and validation to emphasize predicate regulation record requirements.

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