ADVANCED INSTRUMENTS

Pharma & Biotech:

How labs achieve data integrity

Lack of data integrity can be a key reason for breaching compliance in the Pharma and Biotech industries. Shweta Nair, Sr. Product Manager – Biotechnology at Advanced Instruments, explains how important it is for companies to be compliant with data integrity and to ensure the trustworthiness and reliability of electronic records.

In 2017, 65% of all warning letters from the FDA (US Federal Food & Drug Administration) cited data integrity issues. The main concern was incomplete data. By 2021, the most cited regulation of 2020 was 21 CFR Part 211.192, which deals with ‚investigations of discrepancies.'[1,2,3] This situation indicates that the healthcare industry remains in a struggle to fully understand how to conduct effective investigations for unexpected results. Moreover, it shows that non-compliance and lack of knowledge of basic GMP guidelines are still an issue.

US and EU regulatory authorities have defined the criteria for ensuring trustworthy and reliable electronic records in computerized systems via a process known as compliance with data integrity. Regulations and standards such as 21 CFR Part 11, EudraLex Vol 4. Annex 11, GMP, and ISO 17025 establish controls for the use of electronic data systems, with the goal of reducing errors, simplifying processes and reinforcing compliance. The highest risks when not working in a compliant manner lie in import bans, product recalls or even the closure of production plants.

What is data integrity?

Data integrity is defined as the extent to which all data, whether electronic or paper-based, is complete, consistent, accurate, trustworthy and reliable throughout the data lifecycle – from creation through archival stages and its eventual destruction. Complete, consistent and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, accurate, enduring, complete and consistent (ALCOA+)[4]. Regulatory agencies, as well as the life sciences industry, rely on this data to ensure subject and patient rights in addition to the safety, efficacy and scientific value of clinical studies.

ALCOA+	Attribute	Meaning
A	Attributable	Who performed an action and when? If a record is changed, who did it and why?
L	Legible	Data must be recorded in a permanent durable medium and be readable
C	Contemporaneous	Data must be recorded when it was performed followed by date and time
O	Original	Is the information the original data or a certified true copy of the original data?
A	Accurate	No errors or editing performed without documented amendments
A	Available	Available for review at anytime
E	Enduring	Records exist for the entire period
C	Complete	Data is in a complete state to avoid any re-creation or manipulation
C	Consistent	Data is in a sequential manner with a sign and date and follows GDP for consistency in documentation

Table 1: Ensuring data integrity through ALCOA

How is data integrity regulated?

In 1992, the European Union published the EudraLex Vol 4 Annex 11 Guidelines ("EudraLex Rules Governing Medicinal Products in the EU, Volume 4, GMP, Medicinal Products for Human and Veterinary Use") to complement GMP rules of member states. The goal of EudraLex Vol 4 Annex 11 was to ensure product quality and efficacy in the pharmaceutical and biotech manufacturing industries with no increased risk when a computer is used in place of a manual operator. Due to the increased use and complexity of automated systems, EudraLex Vol 4 Annex 11 was updated in 2011 to include all GMP-relevant computerized systems[5].

Electronic signature and record-keeping requirements are laid out in 21 CFR part 11 and apply to certain records subject to records requirements set forth in FDA regulations, including parts 210, 211, and 212. (For more information, see guidance for industry 21 CFR Part 11, Electronic Records; Electronic Signatures — Scope and Application[6].) The guidance outlines the FDA's current thinking regarding the narrow scope and application of 21 CFR part 11 pending their re-examination of 21 CFR part 11 as it applies to all FDA-regulated products. For more information check out our data integrity page on eu.aicompanies.com.

What are the differences between EudraLex Vol 4 Annex 11 and 21 CFR Part 11?

While there are many similarities between EudraLex Vol 4 Annex 11 and 21 CFR Part 11, the two documents are also quite different. To begin, EudraLex Vol 4 Annex 11 and 21 CFR Part 11 diverge in philosophy. Both documents are guidance for good manufacturing practices and cover the same topic: the use of computerized systems in regulated activities. However, 21 CFR Part 11 is a regulation, while EudraLex Vol 4 Annex 11 is a guideline for managing electronic data or computer systems. This means that while EudraLex Vol 4 Annex 11 is strongly recommended for all veterinary and human products produced or sold in the EU, it is not a legal requirement. In contrast, 21 CFR Part 11 is a US federal regulation with fully enforceable requirements that emphasize identity verification, accountability of actions by authorized individuals and reporting obligations.

Another difference between these documents is the respective objective. The approach of 21 CFR Part 11 is to make clear there are requirements to be met to conform to regulations; the emphasis is on activities and reporting. In contrast, the approach of EudraLex Vol 4 Annex 11 is to make clear how to conform to its rules. EudraLex Vol 4 Annex 11 is a detailed guide to the areas of compliance that need documentation, and thus it helps the management of risks.

Moreover, 21 CFR Part 11 discusses only GxP systems, whereas EudraLex Vol 4 Annex 11 also covers areas such as validation, risk manage-

ment, IT security, documentation and supplier service. A further significant difference between these documents is their approach to risk management. EudraLex Vol 4 Annex 11 points to risk assessment as the start of compliance activities. 21 CFR Part 11 differentiates security for open and closed systems, with extra security measures for open systems but without reference to risk or criticality[7,8].

	EudraLex Vol 4 Annex 11	21 CFR Part 11
Scope/ Principal	Computerized systems as part of GMP regulated activities. Application should be validated. IT infrastructure should be qualified.	E-records and e-signatures as used for all FDA regulated activities.
Focus	Risk-based quality management of computerized systems.	Using e-records and signatures in open and closed computer systems.
Objective	Using a computerized system should ensure the same product quality and quality assurance as manual systems with no increase in overall risk.	E-records and e-signatures should be as trustworthy and reliable as paper records and handwritten signatures .

Table 2: High level mapping of EU Annex: 11 vs 21 CFR 11

Which organizations does 21 CFR Part 11 apply to?

21 CFR Part 11 applies to all US-based pharmaceutical companies as well as to the companies that want to sell their products in the US. These include drug manufacturers, biotech companies, medical device organizations, contract research organizations (CROs) and several other FDA-regulated industries (such as food and beverage manufacturing). Additionally, some organizations that are not FDA-regulated may choose to use 21 CFR Part 11 as a guide to assure that they are utilizing good processes for managing their electronic training records and other documents.

Which organizations does EudraLex Vol 4 Annex 11 apply to?

EudraLex Vol 4 Annex 11 is a guideline for computerized systems for countries in the European Union that manufacture and sell medicinal products for human and veterinary use. Computerized systems include software, hardware, validation, operations, supply and service providers, risk management and electronic signatures.

How do you achieve data integrity?

Data integrity is paramount to ensure the validity of data and its analyses. When data is altered in an electronic record system, the original data

must remain visible within the system. The number of users who can alter the data must be limited. There must be an automatic audit trail that records the date, time and source of every entry, decision or change in the data, all of which cannot be controlled by an individual user. Additionally, the system must be tested and validated[9].

The following are important record characteristics needed to achieve data integrity:

1. The data must be retrievable and identifiable;
2. The data must be attributable to a specific subject;
3. Data alterations must be identifiable via audit trails, including information as to who altered the data, why it was altered and when;
4. There must be the ability to reconstruct the trial.

Implementation of data integrity compliance includes electronic records, electronic signatures, system validation and the validation of the supporting systems involved in the processing of electronic data[10].

What is an e-Signature? If you have e-Signatures, do you have to comply with e-record requirements?

According to 21 CFR Part 11.3 (7) , "Electronic signature means a computer data compilation of any symbol or series of symbols executed, adopted or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature." When signatures are executed electronically, then compliance is needed. E-signatures should be permanently linked to the respective record and should include time and date of their recording. Use of e-signatures implies that a system is an e-record system and must be in compliance with all provisions of 21 CFR Part 11.

What are the benefits of maintaining Data Integrity?

Organizations benefit from

- reduced costs by removing manual and paper processes while improving workflow processes;
- reduced costs of managing and documenting their entire record lifecycle, from routing and approval workflow, version control, and comparison to audit trails and reports;
- improved traceability – e-records are simpler for gathering, filtering and presenting information for internal use or FDA audits;
- stronger control over users' ability to design, amend and approve forms;
- better management of global data, including product data, symbols, graphics and languages;
- compliance with data integrity requirements.

What are some examples of systems that are critical to Data Integrity?

Data integrity is related to the trustworthiness of the e-records generated/managed by critical systems. EU and US regulatory authorities are most concerned about systems that are involved with product distribution, product approval, manufacturing and quality assurance because these systems pose the most risk in terms of product quality and/or public safety.

What records does 21 CFR Part 11 apply to?

This regulation applies to all aspects of the research, clinical study, maintenance, manufacturing and distribution of medical products. 21 CFR Part 11 covers[11]:

- required records that are maintained in an electronic format in place of a paper format;
- required records that are maintained in an electronic format in addition to a paper format and that are relied on to perform regulated activities;
- records submitted to FDA in an electronic format;
- e-signatures that are intended to be the equivalent of hand-written signatures.

For which activities does EudraLex Vol 4 Annex 11 require validation?

EudraLex Vol 4 Annex 11 requires validation for activities including[12]:

- Production
- Material supply
- Lab testing
- Process controls
- Quality systems
- Clinical trials
- Records and documents
- Product releases and distribution
- Product storage

When does an audit trail begin? Should execution of a signature be audit trailed?

Audit trail initiation requirements differ for data and textual materials. For data, if you are generating, retaining, importing or exporting any electronic data, the audit trail begins from the instant the data hits the durable media. For textual documents, if the document is subject to approval and review, the audit trail begins upon approval and release of the document. Additionally, execution of a signature must be audit trailed.

What type of reporting capability on audit trail data should be supported?

According to US 21 CFR Part 11 §11.10 (e), audit trails must be secure, computer-generated and time stamped to independently record the date and time of operator entries and actions that create, modify or delete e-records. Such audit trail documentation shall be retained for a period at least as long as that required for the subject e-records and shall be available for agency review and copying. Audit trails should indicate record changes and provide the date and time, along with the rationale for such changes, as part of Good Laboratory Practice.

What must a vendor do to claim that their hardware and software are 'compliant' with 21 CFR Part 11?

No vendor can claim that their software products are certified 21 CFR Part 11 compliant. A vendor, instead, can say that they have all of the technical controls for data integrity compliance built into their product. However, it is the responsibility of the user to implement the procedural and administrative controls (both correctly and consistently) along with using products with the correct technical controls for overall data integrity compliance.

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Sources:

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