A Guiding Light

Lack of data integrity is a key reason for breaching compliance. Shweta Nair at Advanced Instruments sat down with Angela Bazigos, CEO of Touchstone Technologies Silicon Valley and a co-author of 21 CFR Part 11 FDA guidelines to evaluate this

In 2017, data integrity issues were cited in 65% of all FDA warning letters. The main reason was incomplete data. In the pharmaceutical and biotechnology industries, this can be prevented by ensuring the trustworthiness and reliability of electronic records, a process that is also known as compliance with data integrity. The highest risks, when not working in a compliant manner, lie in import bans, product recalls, or even the closing of production plants.

The FDA defines the criteria under which electronic records and electronic signatures are considered trustworthy, reliable, and equivalent to paper records in Title 21 of the Code of Federal Regulations (21 CFR) Part 11.

By becoming FDA 21 CFR Part 11 compliant, organisations 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 controls 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

FDA 21 CFR Part 11 allows life science organisations to use e-records and e-signatures in place of paper. However, a piece of software by itself cannot be compliant. Any critical software must be supported by a properly conceived and performed validation project, normally following current GMPs.

Shweta Nair: Which organisations does Part 11 apply to?

Angela Bazigos: Part 11 applies to drug organisations, biotech companies, medical device organisations, CROs, and several other FDA-regulated industries (such as food and beverage manufacturing). Additionally, some organisations that are not FDA-regulated may choose to use Part 11 as a guide to assure that they are utilising good processes for managing their electronic training records and other documents.

What records does Part 11 apply to?

The regulation applies to all aspects of the research, clinical study, maintenance, manufacturing, and distribution of medical products. It covers:

- Required records that are maintained in electronic format in place of paper format

ALCOA	Meaning	Explanation	Comments
A	Attributable	Who performed an action and when? If a record is changed, who did it and why?	Who did it? Source data
L	Legible	Data must be recorded in a permanent durable medium and be readable	Can you read it? Needs to be permanent
C	Contemporaneous	Data must be recorded when they were performed followed by date and time	Was it done in real time?
O	Original	Is the information the original date or a certified true copy of the original data?	Is it original or a true copy?
A	Accurate	No errors or editing performed without documented amendments	Is it accurate?

Table 1: Ensuring data integrity through ALCOA

- Required records that are maintained in electronic format in addition to paper format, and that are relied on to perform regulated activities
- Records submitted to FDA in electronic format
- E-signatures that are intended to be the equivalent of handwritten signatures

What is data integrity?

The completeness, consistency, and accuracy of data. Complete, consistent, and accurate data should be attributable, legible, contemporaneously recorded, original or a true copy, and accurate (ALCOA).

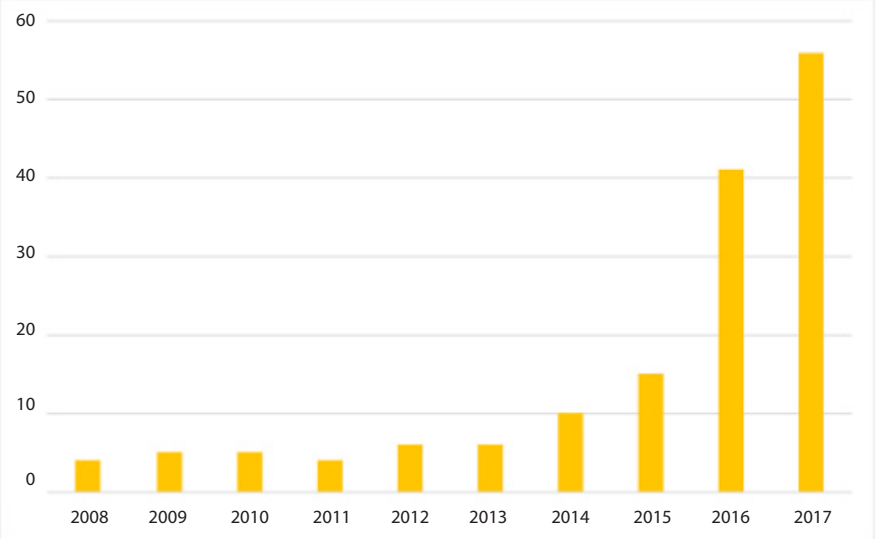

Figure 1: Data integrity associated warning letters, CY2008-CY2017

Is the FDA concerned with data integrity?

Per Edwin Rivera, of the Chief Investigations and Preapproval Compliance Branch at the FDA's Center for Drug Evaluation Research (CDER), one of FDA's biggest concerns is integrity of electronic data. Three of ten recent audits revealed data of highly questionable reliability that are currently under review at CDER. Additionally, the number of FDA warning letters pertaining to data integrity has grown exponentially, as FDA puts more focus on data integrity during inspections.

The FDA plans to continue to increase their focus on data integrity issues with:

1. Specialised training of investigational staff on uncovering data integrity, data manipulation, and fraud
2. Greater focus on data integrity and fraud
3. The agency's commitment to follow up on leads or information regarding data manipulation and fraud

Mr Rivera also gave recommendations to the industry:

1. Train employees on proper handling and reporting of data
2. Assure the reliability of data reported in applications and manufacturing records

How do you achieve data integrity?

Data integrity issues are paramount to ensuring the validity of the data and their analyses. When data are 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 logs in the date, time, and source of every entry, decision, or change in the data that cannot be controlled by the user. Additionally, the system must be tested and validated.

The following are important record characteristics to achieve data integrity:

1. Retrievable and identifiable data
2. Data must be attributable to a specific subject
3. Audit trails identifying who altered the data, why it was altered, and when
4. Ability to reconstruct the trial

Could you define and provide examples of systems that are critical to data integrity?

For Part 11, data integrity is related to the trustworthiness of the e-records generated/managed by critical systems. The FDA is 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 are the main business ramifications of 21 CFR Part 11 on my organisation?

The ramifications include a number of areas:

1. Evaluation of the regulatory impact and the scope of the system. Is it an e-record, e-signature, etc.? The rule includes all records that are generated, stored, or reported, such as attendance records, test scores, and many others
2. Certification to the FDA that a company considers e-signatures to be the legally binding equivalent of traditional handwritten signatures
3. Various SOPs to document establishment of user identity, user accountability, procedures, etc.
4. Audit trail monitoring
5. Validation of commercial and custom software
6. Qualification of personnel developing, administering,

maintaining, or using the system
7. Archiving and retrieval
8. Costs and staffing for all items mentioned above

What is the difference between 21 CFR Part 11 and EU Annex 11?

The relationship between FDA's Part 11 and the EU's Annex 11 (EudraLex rules governing medicinal products in the EU, Volume 4, GMP, medicinal products for human and veterinary use) diverges in philosophy. Both documents cover the same topic: the use of computerised systems in regulated activities. However, the approach of Part 11 is to make clear there are requirements to be met in order to conform to regulations. The emphasis is on activities and reporting.

In contrast, the approach of Annex 11 is to make clear how to conform to its rules. Annex 11 is a detailed guide to the areas of compliance that need documentation. A significant difference is the approach to risk management. Annex 11 points to risk assessment as the start of compliance activities. Part 11 differentiates security for open and closed systems, with extra security measures for open systems but without reference to risk or criticality. The aggregate of these differences is represented visually with the point-to-point comparison matrix shown in Table 2.

What is the difference between a closed and open system?

The agency agrees that the most important factor in classifying a system as closed or open is whether the persons responsible for the content of the e-records control the access to the system containing those records.

A closed system refers to an environment in which system access is controlled by those persons responsible for the content of e-records that are in the system (e.g., inside the company's firewall). An open system denotes an environment in which system access is not controlled by those persons who are responsible for the content of e-records that are in the system (e.g., outside the company's firewall). If those persons do not control such access, then the system is open because the records may be read, modified, or compromised by others to the possible detriment of the persons responsible for record content. Hence, those responsible for the records would need to take appropriate additional measures in an open system to protect records from being read, modified, destroyed, or otherwise compromised by unauthorised and potentially unknown parties.

	Annex 11	Part 11
Scope/Principle	Computerised 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 computerised systems	Using e-records and signatures in open and closed computer systems
Objective	Using a computerised 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 Part 11

FDA-483 observations
Warning letters
Import alerts
Withheld product approvals
Cancellation of government contracts
Product recalls
Seizure
Consent decree of permanent injunction
Civil money penalties
Suspension or revocation of licences

Prosecution (including indictments and temporary or permanent debarment, if found guilty)
Damage to a company's reputation
Loss of sales
Loss of jobs
Loss of share value
Closing or taking over company

Figure 2: What happens if an organisation does not comply with data integrity?

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

According to the FDA, "Electronic signature means a computer data compilation of any symbol or series of symbols executed, adopted, or authorised by an individual to be the legally binding equivalent of the individual's handwritten signature". Certain signatures are required, and if they are executed electronically, then compliance is needed. 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 is the definition of hybrid system? Could you give an example of one?

A 'hybrid system' is defined as an environment consisting of both electronic and paper-based records (frequently characterised by handwritten signatures executed on paper). A very common example of a hybrid system is one in which the system user generates an e-record using a computer-based system (e-batch records,

analytical instruments, etc.) and is then required to sign that record as per the predicate rules (GLP, GMP, GCP). However, the system does not have an e-signature option, so the user has to print out the report and sign the paper copy. Now the user has an e-record and a paper/handwritten signature. The system has an electronic and a paper component, hence the term hybrid.

If using a hybrid system approach to e-signatures, how do you link the handwritten signature to the e-record?

Since Part 11 does not require that e-records be signed using e-signatures, e-records may be signed with handwritten signatures. If the handwritten signature is applied to a piece of paper, it must link to the e-record. The FDA will publish guidance on how to achieve this link in the future, but for now it is suggested that you include in the paper as much information as possible to accurately identify the unique electronic record (e.g., at least file name, size in bytes, creation date, and a hash or checksum value). However, the master record is still the e-record. Thus, signing a printout of an e-record does not exempt the record from Part 11 compliance.

What is the FDA's view on date and time? Is it not mandatory that it is local?

The agency has reconsidered their position on local date and time stamp requirements. The FDA guidance states, "You should implement time stamps with a clear understanding of what time zone reference you use. Systems documentation should explain time zone references as well as zone acronyms or other naming conventions".

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

Audit trail initiation requirements differ for data vs textual materials. For data, if you are generating, retaining, importing, or exporting any electronic data, the audit trail begins from the instant the data hit 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 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 say who did what to your records and when – why for GLP. Part 11 does not specify the format for audit trials. This should be discussed in a forthcoming FDA guidance document for Part 11 audit trails.

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 Part 11 compliant. Instead, a vendor can say that they have all of the technical controls for 21 CFR Part 11 compliance built into their product, but remember, 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 Part 11 compliance.

References

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About the authors

Angela Bazigos is the CEO of Touchstone Technologies Silicon Valley, a firm dedicated to providing expert compliance consulting and support services to pharma, biotech, medical devices, CMOs, and CROs. Angela is a co-author and prototype contributor of 21 CFR Part 11 guidance with the FDA. She continues to collaborate with the FDA on new guidance documents.

Shweta Nair is the Senior Product Manager, Biotechnology portfolio, at Advanced Instruments, a manufacturer of scientific analysers that serves the biotech and pharma industries. The company recently launched a portfolio of osmometers that include data integrity features in support of 21 CFR Part 11 and EU Annex 11 compliance.