AN IN-DEPTH EXPLORATION OF TITTLE 21 OF THE CODE OF FEDERAL REGULATIONS, PART 21: COMPREHENSIVE REGULATIONS GOVERNING ELECTRONIC RECORDS AND DIGITAL SIGNATURES

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ABSTRACT

All Procedures are required to be fully documented and reported to regulatory authorities such as the U.S. Food and Drug Administration (FDA). The paper-based study records are increasing in size in order to document every single element as the criteria for documentation are continually increasing. However, the approach is to transfer the data to the database, but for every protocol, the specific database is required. Hence, at the moment, it hasn't been feasible to develop generic electronic database that can be used for every single study to act as the source of documentation. They have devised a plan that involves using a user tool to document sources in a way that mirrors the advantages of traditional paper recordkeeping methods closely. Of paper documents we utilize tablet devices to store data, on servers using components and software. In our system setup we follow the regulations set by the US FDA for maintaining records. Our approach includes implementing a graphical source documentation technology that mimics the benefits of paper record keeping practices effectively. We use tablets of paper to store data, on servers in our system with components and software options available to us as, per the regulations established by the US FDA for managing electronic records.

Key words: Electronic signature, electronic record, closed and open system.

Introduction

The purpose of this document is to outline the FDAs understanding of how part 11 of the Code of Federal Regulations Title 21 which pertains to electronic signature and electronic record applied, executed. It is intended for individuals who maintaining records or providing information to the FDA as part of a regulatory mandate and have opted to do electronically thus falling under the jurisdiction of part 11. Section 11 pertains, to documents produced or altered while carrying out the agency's record keeping obligations as outlined in its regulations. Section 11 also covers documents sent to the agency in accordance, with the FD&C Act and PHS act, these records are not explicitly mentioned in guidelines. The key legal standards outlined in the act and FDA regulation are termed as rules, within this guide.

In order to maintain the quality of animal medications and biologics effectively and ensure compliance, with the Current Good Manufacturing Practice (CGMP) the FDA is conducting an evaluation of part 11 concerning all FDA regulated products. Our next step involves initiating adjustments to part 11 subsequent to this

evaluation process with the aim of providing an understanding regarding the scope of part 11 application. It is important to note that we will be exercising flexibility, in enforcing part 11 requirements while we continue our review and assessment of part 11 regulations.

In accordance, with this guidance documents instructions provided here. We do not intend to enforce compliance with the validation processes or record keeping criteria outlined in part 11 strictly. The regulatory authority may proceed with enforcement actions in cases of noncompliance, with the regulations; however, it is essential to maintain and produce records in alignment with those standards regardless.

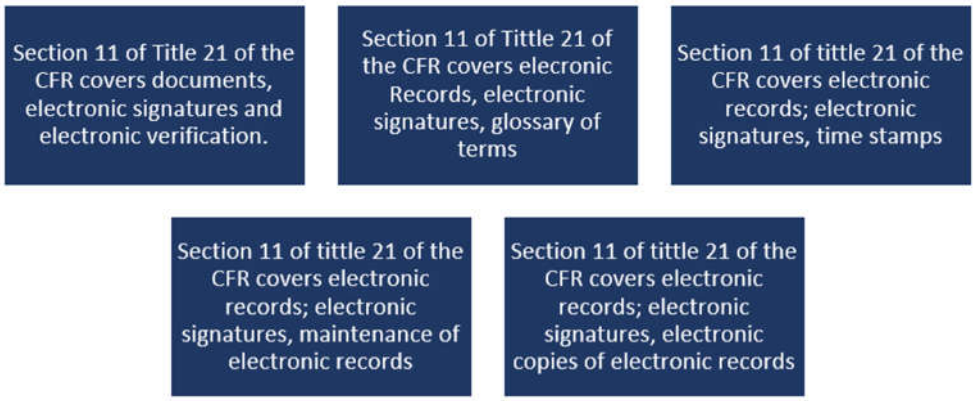
The FDAs guideline publications do not create responsibilities; instead, they offer the agency's stance and should be viewed as recommendations unless backed by explicit legal or regulatory requirements. The use of "should", in agency guidelines suggests a suggestion or proposal, then a mandate. [1]

Context

The final part 11 regulations, from the FDA were issued in March 1997. Outline the standards for records and signatures to be considered as valid as their paper counterparts, under certain circumstances in order to protect public health effectively across all FDA program sectors and promote the extensive adoption of electronic technology.

There have been discussions and disagreements regarding how the rules are understood and put into practice by contractors and industry professionals since section 11 was implemented in August 1997.The FDA has taken steps to explore potential concerns related to part 11 by addressing the topic at various conferences and engaging with industry groups and other stakeholder's multiple times. They have also released a compliance policy guide called CPG 7153.17 which outlines their approach, to enforcing regulations on records and signatures in accordance, with 21 CFR Part 11. Several preliminary instructional papers have been released to the public recently; one of them is depicted in figure 1.

There have been worries raised in these discussions that some ways of understanding the regulations in part 11 could stifle creativity and progress, in technology without providing a health advantage to the public; this might lead to higher compliance costs than what was initially anticipated when the rule was created and impose unnecessary limitations on electronic technology that do not align well with the FDAs intended purpose, for issuing the rule. The guidelines, for validating information and maintaining



records have raised concerns regarding the handling of legacy systems and data retention protocols.

Due, to these worries we had about this matter and other related topics in part 11 documents based on the agency's CGMP plan led us to take a look at them. We announced the removal of the industry guidance on records and signatures under 21 CFR Part 11, in the Federal Register dated February 4th of 2003 (68 FR 5645). We had made a decision to reduce the amount of time industry spends reviewing and providing feedback on the guidelines as they might not align with our approach, in the CGMP project anymore. On February 25th in 2003 (68 FR 8775) we announced that the draft guidance documents related to part 11 on validation procedures and terminology definitions well as topics like time stamps and managing electronic records were no longer in effect along, with the withdrawal of document CPG 7153;17. We have taken into account the input, from the public regarding these guidelines and will use it to inform our future decisions regarding Part 11 regulations and policies moving forward. There are currently no intentions to release revised versions of these draft guidelines or the Compliance Policy Guide (CPG). [(1)]

An outline of important aspects of 21 CFR Part 11

The final regulations include the following sections:

SECTIONS	TITTLE
A	General provision
B	Electronic record
C	Electronic signature

TABLE 1: SECTIONS OF CFR 21 PART 11

The introductory section contains remarks, from the draft of the 1994 regulations and their interpretation stressing the significance for all parties engaging with it to carefully review and grasp the content outlined in table 1.

Adherence, to signatures is also optional; however, it is important to mention that Part B includes specifications for signatures and Part C addresses issues concerning documents as well. Therefore, it is highly recommended to take an approach, towards records and signatures.

Goals of the regulations

The main objective of the Act is to guarantee the reliability and trustworthiness of record and electronic signature systems by addressing concerns regarding the misuse of text editing tools to alter electronic records without proper identification and tracking protocols, in place as recognized by FDA.

Electronic signature wants to carry the weight and importance as traditional hand written ones do despite their ease of use and simplicity, in operation According to the FDAs concerns electronic signatures might not be treated with the level of seriousness as handwritten ones which is why various training and control measures to ensure the non-repudiation of electronic signature.

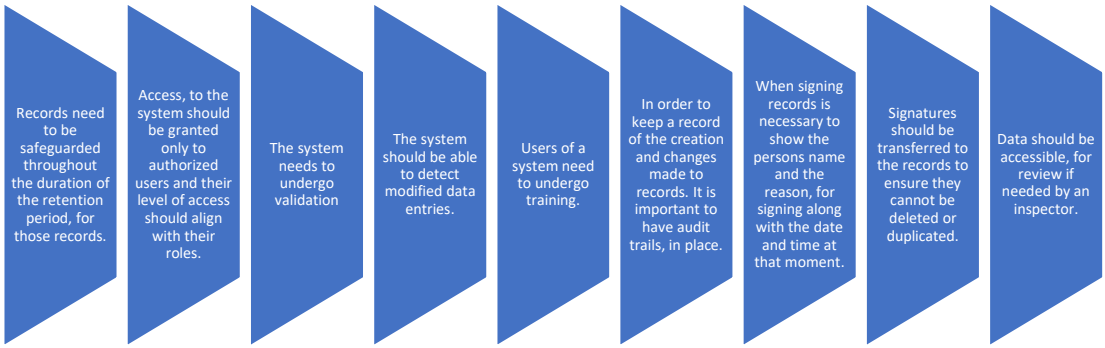
The rules are basically the requirements and they mention ", at least" several times. But most organizations think that's all they need.

Key definitions

This overview provides three definitions: electronic records, electronic signature, and closed system.

Electronic record:

Every content comprising text along, with images or data stored digitally by a computer system is categorized as a record.



This definition underscores the points outlined below:

- The description is quite extensive.
- The phrase " forms of data representation" pertains to records, in various forms. Be it existing or yet to be created or utilized.

Electronic signature:

An electronic signature refers to a record of symbols or a combination of symbols that is created or approved by a person to serve as a valid substitute, for their handwritten signature.

In this scenario the term "electronic signature" is used broadly as the law covers references to biometrics and digital signatures presenting both definitions here.

1. Biometrics is a way to confirm someone's identity by measuring their features or behaviour's.
2. An electronic signature is generated using techniques or authentication, from the originator through a specified set of rules and criteria to confirming the identity of the owner and guarantee the contents integrity.

Closed system:

In a system access is controlled by designated individuals who're responsible, for the content of electronic records stored within the system.

The main aspects highlighted in this description are;

- The system is mentioned, the regulation does not refer to any application.
- "System refers to a scope that encompasses the IT infrastructure, which historically was not considered in assessments". (2)

Electronic records

In order for electronic records produced by a computer system to be deemed reliable and trustworthy under the law' various safeguards are put in place to ensure these criteria is met'. To sum up' the main guidelines are outlined in figure 2.

Electronic signatures

Section C of the guideline includes guidelines, for administrative measures along with some technical specifications as well. Even though complying with Section C of the guideline is optional. Each organization can decide whether to adopt signatures or not many security requirements are equally important for electronic records such as detecting unauthorized system access, at 11:300. The

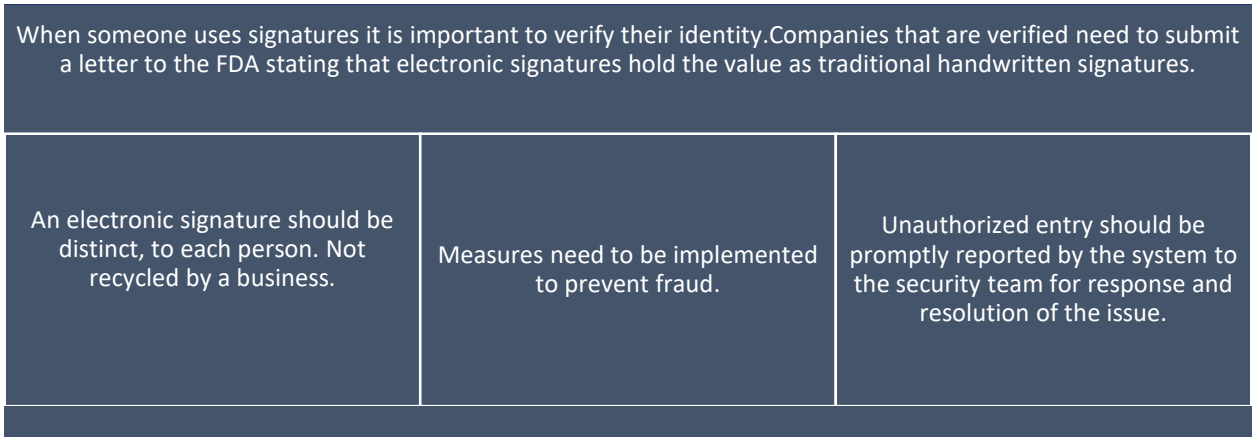


FIGURE 3: MAIN REQUIREMENTS OF ELECTRONIC SIGNATURES

specific requirements are outlined in figure 3.

There are three types of signatures in bioanalysis that are mentioned in the figure 4 that can be utilized.

The influence of 21 CFR Part 11, on bioanalytical laboratories

When the regulations of 21 CFR 11 came into effect at laboratories in the past. Not all systems were following the rules correctly. This led to issues such, as;

- There is a lack of a audit or only a insufficient audit trail available.
- Limited/ lack thereof.
- Rewriting a file, with or, without notice with no trace of the data.
- We do not accept signatures.

Systems that were, in operation when the regulation came into effect and are still in use now are not meeting compliance standards; they are referred to as systems due to their combination of records and hand-written signature attached to the paper copies of those record. It is challenging to match the signed paper documents with their corresponding records, in these systems and it is advisable to upgrade them to fully compliant systems promptly to address this issue.

In labs individual workstations storing electronic records pose a considerable risk due, to the need for consistent backups to safeguard the data in case of disk failure. Nevertheless, the cost of maintaining these records could be excessive. Pose a security risk since altering timestamps on a workstation is relatively simple. It would be

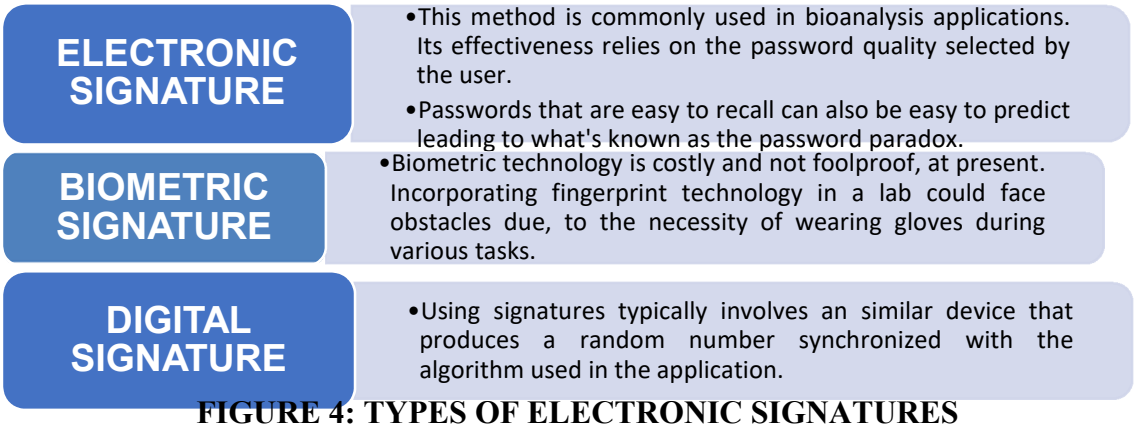


FIGURE 4: TYPES OF ELECTRONIC SIGNATURES

more advisable to have the data networked so that the IT department can manage it using equipment and systems.

The regulations, under 21 CFR 11 also apply to the IT department since they specifically refer to systems than applications in the guidelines provided. The IT team must ensure they operate in accordance, with these regulations and have documented procedures supported by evidence of their actions. (2)

Advantages of CFR 21 Part 11

Reworked processes are crucial, for leveraging the benefits of 21 CFR 11 through operations in organizations to achieve business advantages. Investigating and reassessing your procedures can lead to savings in costs and time investment by identifying areas for improvement and optimization. Through an evaluation of your operations, you can uncover opportunities, for enhancing efficiency and productivity that result in cost savings and time efficiencies. Advantages of CFR are included in figure 5. (2)

How does laboratory automation software affect developers in their work?

Preserving the accuracy and security of records is crucial, to their maintenance and protection of information if applicable in a closed system where only authorized personnel have access, to the content of the records**.**

- "To ensure precision and reliability while maintaining performance as intended and the ability to detect any inaccurate data entries " systems need to undergo validation.
- Records need to be stored in a way that permits the FDA to review them in ways readable, by humans, for inspection or reproduction purposes.
- If the older hardware is no longer, in use or kept up to date with maintenance procedures in place to ensure it remains operational and compatible with systems and software updates. The data stored on legacy systems should still be retrievable or easily accessible in a format that can be understood and utilized without

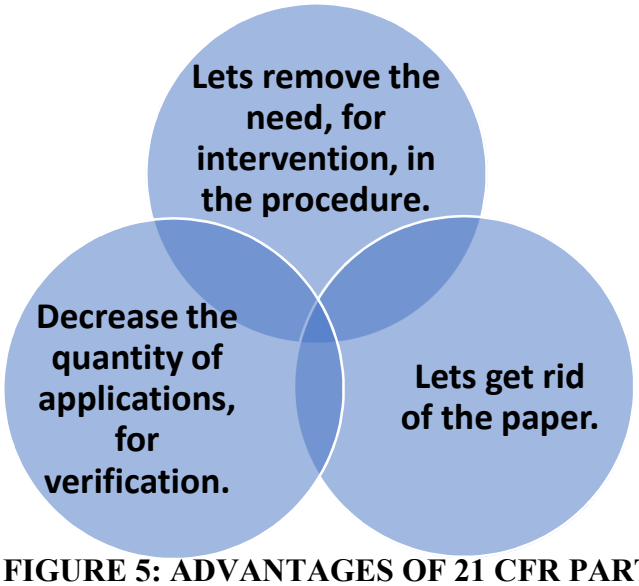


FIGURE 5: ADVANTAGES OF 21 CFR PART 11

any issues, during the process of system replacement or upgrades.

- When making changes or updates, to systems it's important to take this into account.
- It is important to maintain records, for the duration as their paper counterparts they are replacing in order to comply with regulations and standards. When operators perform actions that involve creating or modifying records or deleting them altogether it is crucial to have these actions documented independently through computer generated audit trails that include a timestamp indicating the time the action was taken.
- These audit trails should be designed in a way that does not overwrite recorded data. In situations where systems operate in time zones it is recommended by authorities that timestamps should include a reference to the time zone and appear in formats that are easily understandable, by humans.
- It's crucial to follow the sequence of events or stages in a process whenever.
- Only individuals granted permission should have the ability to sign paperwork access the system and modify existing records.
- All changes and updates to system documentation must be done in an order. Documented with an audit trail.

When considering a system labelled as "open " such, as email records or web-based applications these specific factors should be considered well.

- To preserve confidentiality, encoding documents may be necessary.
- Using signature standards ensures that records are secure and trustworthy.

Evaluation of a signatures

- Every time you sign a document make sure to include your name, date, time of signing. Also remember to indicate the significance of your signature, like whether you're approving or inspecting a record.
- This data should be included in all documents that have been signed and can be understood by people.
- Every handwritten or digital signature must be linked to the corresponding record to safeguard against duplication and misuse.

Biometrics, like fingerprints or retinal scans are not required as the basis, for signatures; usernames and passwords are also considered acceptable but must meet certain criteria;

- You need to use two different types of identification methods.
- When a user signs documents, in one session they must use least one component, for each document.
- Though the concept of a " session" lacks a definition the guideline specifies that both elements should be utilized to complete the signature when multiple documents are signed.

While username and password security measures rely heavily upon training and company operating procedures (SOP) there are specific software design considerations that remain important.

- Each username password pair must be unique.

- It's best not to use the usernames, which is already used.
- Make sure to update your passwords.
- To uncover and reveal any compromised user credentials, like usernames and passwords safeguards need to be established disable the combination and inform the management or system administrators. (3)

The connection, between computer system validation and compliance, with 21 CFR Part 11.

Rule 21 CFR part 11 was introduced into regulations, by the FDA in 1997 with a focus on implementing administrative measures for electronic signatures and setting limits on the utilization of electronic records as well as paper records replacement eligibility and the equivalence of signature to hand-written ones, in terms of safety and enforceability.

Despite using signatures technology advancements 21 CFR part 11 impacts all companies using computer systems that create records tied to the GMP setting. Every computer system falling into this category requires both technical controls to ensure; The ability to generate thorough record copies, Time stamped audit trails are accessible to guarantee records are secured for accurate and swift retrieval Authority checks are enforced while maintaining proper system access. (4)

Importance of electrical signatures

The digital signature is created by assigning a username and password, along, with a date and time stamp that encompasses its significance (like approval responsibility or authorship).

Our main administrative tools, for the file server handle authentication by utilizing a signature file located outside of Adobe 9 of within the application folder itself Users get to pick their passwords and usernames which are then updated in the active directory system.

By incorporating signatures alongside digital signatures promotes the integrity of the signing process even further and helps prevent misuse of login details for creating digital signatures using handwritten ones instead. Moreover, the FDA has recognized the need for a specific definition of signatures to cater to individuals looking to integrate paper and electronic systems in their record keeping processes. This decision allows for the use of signatures, in formats. For example, according to the FDAs guidelines; "A handwritten signature is considered valid if the signing process, with a stylus is saved when done on a device." If this signature is later printed on paper, it does not change the method used to sign. (5,6)

Conclusion

In conclusion we've developed a system that mirrors the paper-based setup, for clinical research study records. Our approach offers advantages in terms of organizing and accessing files efficiently. A major perk of electronic systems. While embracing the benefits of graphical paper documentation for authenticity and reliability it serves as the primary source material, for our system. Data needs to be transferred by hand onto case record documents that are currently stored in databases. To the traditional paper systems that electronic setups replicate. There's an added layer of data handling involved when information is manually moved to case record forms. Redundant safeguard measures are put in place by having data recorded both in the source and the case record form. However, transferring data manually demands effort. Raises the risk of

errors occurring. The upcoming challenge will involve automating the extraction of data, from our document and converting it into a database format by updating field labels accordingly at present time The process is underway to make sure the source template can seamlessly transition into a database setup Integrating visual data into the database is another milestone, in progress As contemporary databases primarily rely on text inputs only this particular task proves to be more intricate However there is a way to input graphical data into a database format and save it for future reference. Our focus, for research is centred around enhancing our ability to capture information and save it in a database that can be easily searched through.

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