

Risk-Based Approach to 21 CFR Part 11

The 21 CFR Part 11 regulation is a comprehensive piece of legislation that outlines the controls necessary for the regulated industry to utilize electronic records and electronic signatures.

Without careful interpretation, however, the requirements can lead to over-engineered solutions that adversely impact the productivity of the industry without providing added benefit to patient health. The goal of this paper is to provide the philosophy necessary to apply risk management, and to encourage manufacturing innovation and technological advances. This philosophy is based on the ideas in the new FDA cGMP initiative. We believe that this approach is equally applicable to all FDA regulated industries.

We are currently working on more detailed material based on the philosophy presented here, covering all sections of 21 CFR Part 11 but focusing on key areas. This material includes more detailed definitions, specific processes for defining risk and identifying appropriate controls, and implementation examples. We will present this material for your consideration in the near future.

The key areas of the regulation which require attention are:

- The definition of an electronic record
- Audit trails
- Electronic copies for inspection
- Retention and maintenance of records
- Hybrid and procedural solutions
- Application of electronic signatures

The use of a risk-based approach to Part 11 would allow the regulated industry to analyze their processes, identify GxP records, and implement appropriate controls to mitigate risks.

The suggested risk-based approach has the following steps, that cover both the scope and selection of appropriate controls:

- User firms identify and define GxP electronic records and signatures, based on the predicate rules, criticality of the process, and risk to product safety, efficacy and quality.

- User firms implement controls commensurate with the criticality of the electronic record, and risks identified for that record. These controls should be documented and justified with reference to the identified risks.

This is a top-down approach (“is it a GxP record?”), rather than a bottom-up approach (“is it an electronic record?”). This approach focuses on the critical records as opposed to all electronic records created by a firm.

Definition of Electronic Record

Reference: 21 CFR Part 11.1 (b).

The current interpretation of what is in scope is too broad. This leads to a potential stifling of innovation, and draws focus away from the most critical areas. This is not in the spirit of a risk-based approach.

User firms should identify and define the high impact GxP electronic records and signatures, based on the predicate rules, criticality of the process, and risk to the quality, safety, identity, purity, or strength of the product.

The focus of effort should be on records that have a high impact, i.e. those records upon which quality decisions are based. Examples of high impact records are batch records and laboratory test results. Examples of records with low impact include environmental monitoring records not affecting product quality, training records, and internal computerized system information such as setup and configuration parameters.

Existing security measures and established validation measures are more than adequate to ensure the integrity of lower impact records – additional Part 11 controls are cumbersome and add very little value.

Internal system information not identified in the predicate rules is low impact. The integrity of this information can be assured by system validation, change control, configuration management, and routine security features. These may be controlled by a suitable established procedure – additional Part 11 controls are not required. Paper records of such events are acceptable.

Software should not be considered as being GxP electronic records with regard to Part 11. Industry and FDA have worked for many years on developing approaches for dealing with hardware and software in the GxP environment based on validation of systems, configuration management, change control, and adequate procedures and plans for maintaining the validated state. These approaches have been widely adopted and very successful in meeting GxP requirements. Considering software as GxP electronic records has little practical benefit, as well as discouraging firms from adopting innovative technological solutions. It should be noted that not considering software as a GxP

electronic record is in conflict with CPG 7132a.11 “CGMP applicability to hardware and software”.

Copies of Electronic Records

Reference: 21 CFR Part 11.10 (b).

The user firm should provide an investigator with reasonable and useful access to records during an inspection. The provision of electronic copies under Part 11 can bring significant technical challenges, especially for complex systems. We propose that user firms should be able to meet the requirement for accurate and complete copies by, in order of preference:

- Using industry standard portable formats where possible, if the use of such formats brings more benefits than disadvantages.
- Utilizing established automated conversion or export methods where available, to make copies in a more common format (e.g. PDF or paper copies).
- Allowing inspection and review of records on the firm’s site, using the firm’s hardware and software, following the firm’s established procedures and techniques for accessing those records.

The key concepts are that the content and the meaning of the GxP records are preserved during copying, and that these GxP records are available in human readable form.

Retention and Maintenance of Records

Reference: 21 CFR Part 11.10 (c).

Archiving of electronic records can be problematic in two main ways: volume and processability.

If the definition of Part 11 scope is clarified, and interpreted according to a risk-based approach, then volume ceases to be such a significant problem. For example, an encapsulation machine with a check-weigher can measure two million capsule weights for a single batch. The batch record may only use these values to generate a curve that shows the batch weight distribution falls within validated norms. Only the weight distribution curve is meaningful and the individual data points need not be archived, provided the generation process of the distribution curve is validated. This meets the expectation of the predicate rule 21 CFR 211.188, yet considerably eases the record-keeping burden.

Archived records must be retrievable; it is not, however, always necessary to reprocess electronic records. The content and meaning of retrieved records must be evident.

Archiving to non-electronic media such as microfilm, microfiche, and paper, is an acceptable alternative to electronic media in some cases, as long as the content and meaning of the electronic record is not compromised, and the archiving process is validated.

Printing copies of records held electronically, and reviewing and subsequently approving them by means of a handwritten signature, to produce the master regulatory record for long term keeping can be effective and efficient. The user firms must ensure that any contextual and background information required to interpret the records is also kept. For high impact records it may be essential that electronic copies of the record are also retained – although not necessarily in reprocessible form.

Reprocessability is an additional challenging requirement placed on user firms when using electronic records. It should be the exception, rather than the rule. Those records needing reprocessability should be clearly identified and defined by the user firm, based on risk. For clinical records, reprocessability may be important, but not for manufacturing records where the main requirement is to support integrity and reliability of the records.

In most cases the value of the ability to reprocess records decreases as time passes. When a product is relatively new to the market there may be a host of issues not well understood, such as unusual drug interactions or environmental factors. The ability to analyze clinical data for new drug products based on new information gleaned from post-market reporting is important. However, as the product is used for several years without major problems, a profile begins to emerge of the drug as safe under normal conditions of use.

A risk-based approach should be used in deciding whether to migrate older records to a new format. Based on risk assessment data, a decision would be made whether it is important to retain processability of older data. If risk is sufficiently low, the firm may choose to write the records to a common, simple, permanent format for archival (PDF, microfiche, paper, etc.). The GxP records and their context and meaning are retained, and the key elements such as the audit trail can be captured and retained. The principal compromise accepted here is sacrifice of the ability to *easily* search and manipulate the records.

Audit Trails and Data Security

Reference: 21 CFR Part 11.10 (e).

Currently the audit trail requirement is being applied too widely. Audit trails should be applied only in cases where operator actions create, modify, or delete high impact GxP records.

If risk analysis shows that adequate data integrity can be achieved through rigorous security controls, user firms should be expected to take a justified decision that addition of audit trails does not provide significant benefit. Audit trails would still be important

for systems in which the users are expected to modify data as a routine part of the business process.

We realize and agree that security and integrity of data is of key importance. Audit trails are only one mechanism for ensuring data integrity, together with other physical, logical, and procedural security measures. Data integrity is also supported by established validation methods that prove system operation and data integrity features, and robust change control that maintains the control established by validation.

In many cases where the data should not be modified, the ability to do so can be restricted such that audit trails are not required. For example, if an HPLC data system writes to a secure directory, and validated system controls do not allow overwriting of files, an automated audit trail adds little to the integrity of this data.

Current industry security practice fulfils many of the Part 11 requirements for data integrity. User firms should be encouraged to follow existing international standards, such as ISO/IEC 17799 *Code of practice for information security management*, and their existing information security policies, as well as generally accepted good Information Technology practice.

Procedural and Hybrid Solutions

Reference: 21 CFR Part 11.10, 21 CFR Part 11.70, and others.

The continued use of hybrid systems, where electronic and paper records and signatures co-exist, does not increase the risk to the product or patient, if adequate procedural controls are established. Such procedural controls are the basis of current GxPs, and should be acceptable in this area also.

Recent draft FDA guidance on 21 CFR Part 11 has concentrated on complex technical methods of linking records to each other and to handwritten signatures. We suggest that in many cases procedural controls are sufficient, and effective. Procedural links are extensively used elsewhere in the GxP environment. For example, records, documents, and materials are related to each other by means of a batch number or component code. Such procedural controls are indeed the bedrock upon which the GxPs are based. The user firm should ensure that procedural controls are established and effective, and that validated system features also mitigate the risk to stored electronic records of unauthorized, or uncontrolled, change, copying, or loss.

Electronic Signatures

Reference: 21 CFR Part 11.100.

User firms should define where they need to apply signatures, based on predicate rule requirements, criticality of the process, and risk to the product. User firms should define whether these should be handwritten or electronic.

Where signatures are currently used with paper records, it may not always be appropriate to apply an electronic signature. With paper records, handwritten signatures are applied in two different cases:

1. As a legally binding signature, when there is a regulatory expectation
2. As a convenient way of identifying a person

In the second of these cases, the appropriate electronic equivalent would be the system logging the user-id, or an entry in the audit trail, rather than an electronic signature. Automation of the process may, in some circumstances, remove the need for identification, because sufficient assurance is provided through validation. Signatures should only be mandatory when explicitly required by a predicate rule.

Conclusion

This paper has attempted to demonstrate that applying a risk-based approach to electronic records in a GxP context can lead to controls appropriate to the criticality and impact of those records.

This allows measures aimed at a high degree of integrity to be established for records that directly impact the quality, safety, and efficacy of the product, while permitting a less rigorous approach for records of lower criticality.

This overall philosophy, based on the ideas in the new FDA cGMP initiative, would encourage manufacturing innovation and technological advances without increasing risk to the patient or to product quality.