



The Implications of 21 CFR Part 11 Guidance Document (docket # 00D-1539) on Operators of Chromatography Data Systems

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The archival of analytical data, including spectra and chromatograms, has been the subject of a great deal of attention and debate recently as the full implications of the introduction of 21 CFR Part 11 have dawned on organizations regulated by the Food and Drug Administration (FDA). Compliance with the Rule remains somewhat of a moving target. In order to address this situation and assist industry to correctly interpret the demands of Part 11, the US Department of Health and Human Sciences of the FDA has issued a draft guidance document (docket number 00D-1539). The document is primarily intended for regulated science-based organizations. However, it also offers assistance on Part 11 compliance for FDA personnel, as well as computing software vendors serving pharmaceutical and other industries in the regulated environment (Good Manufacturing Practice, GMP; Good Laboratory Practice, GLP etc.).

While the document focuses on the maintenance of electronic records and issues such as required retention period and record migration, it also has implications for the acquisition and processing of data, such as that generated through chromatography. In considering potential vendors, operators of chromatography data systems (CDS) should take into account how systems address the issues that this latest draft guidance raises. Likewise vendors need to become familiar with the document to ensure systems ultimately support the customer in achieving compliance.

Users of CDS are looking to save time and money by being able to quickly and accurately turn raw data into results, information and then knowledge for better, more timely decision making. If a few seconds can be saved on every run, when the number of runs a laboratory does every year is considered, the benefit of a modern CDS can soon escalate. Of course, the additional revenue generated by getting new products to market more quickly can easily eclipse this return

on investment. Critical though is that the quality and validity of results can easily be established. When selecting a CDS, laboratories need to strike a balance between the need to fulfill productivity objectives and the existence of advanced functionality to ensure data security and traceability.

To quote the latest draft guidance: “If information is inaccurately or incompletely recorded, record maintenance practices will not compensate for these shortcomings.”

Some science-based organizations have chosen to address the issues of accuracy and completeness solely through archival of electronic records. The guidance document makes clear that companies adopting this approach would be advised not to neglect how their systems, such as CDS, handle and track acquired results. It is clear from this statement that the guidance document, as with 21 CFR Part 11 itself, applies to the life span of the data and its associated metadata, referred to in the document as its “record retention period.” From its inception, certain criteria must be met to ensure that the data integrity is maintained and this can only be handled by the system that created that data, which, for the purposes of this article, is the CDS. The guidance presents two potential approaches to ensure data integrity: the “Time Capsule” approach and the “Electronic Records Migration” approach.

The “Time Capsule” approach requires that the data be maintained on the original electronic media and computer system for the duration of its record retention period. While this may be a viable option for some forms of analytical data, it is extremely limiting for a CDS. Legacy hardware platforms are notoriously expensive to support, employing a diminishing number of often outsourced individuals that have retained the necessary skills. Maintenance of these systems can place an enormous burden on Information Service departments. This is compounded when the hardware vendor discontinues product support and laboratories have to rely completely on internal resources.

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Perhaps a more significant issue with this approach is that it can be an inhibitor to laboratories benefiting from an advance in technology. The “Time Capsule” approach requires that the same software revision (and the associated operating system) are maintained for the life span of the records that it acquired. Chromatography is a key analytical technique and generates a significant proportion of a laboratory’s analytical data. System users have come to expect software that is designed to evolve with the market and are keen to take advantage of future software upgrades and the latest functionality. Remaining with old technology for the sake of compliance would ultimately negate the majority of the benefits of purchasing a CDS and could affect a laboratory’s profitability.

A much more viable alternative for most laboratories is the “Electronic Records Migration” approach, whereby a laboratory is able to move with technology and still ensure compliance with Part 11. To take advantage of this model, features must exist in the CDS to ensure data integrity throughout the migration of the system. Section 11.10(b) states that procedures and controls should include “the ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency.” In addition, Section 11.10(e) states “Audit trail records must be retained for at least as long as that required for the corresponding electronic record.” Modern CDS incorporate fully featured audit trail facilities that are permanently linked to the electronic records or log events to either the event log or to a specified file. Ideally, audit trails should be inseparable from the data itself to ensure compliance. Features like built-in copy verification mechanisms and audit trails can ensure compliance throughout the record retention period.

The guidance stresses the importance of ensuring data integrity throughout the copy process. If a system does not have “a built-in copy verification mechanism, such as cyclic redundancy check (CRC)” the copy process itself must be validated to ensure that data integrity is maintained. System validation is often cumbersome but the use of CRCs removes the onus from the CDS user as the system already has ways of ensuring data integrity is assured. In leading CDS available today, cyclic redundancy checking is automated on significant files to detect illegal modifications. For example, the CDS will detect changes made using an external application, such as Microsoft Notepad or Microsoft Word. The data file is then flagged as corrupted and therefore unusable if the check finds an illegal modification.

Section 6.2.1.5 of the guidance document addresses the subject of altered copies that can comply with Part 11 provided that all alterations are documented and compensations are made. One example given in the guidance is the use of colour codes. For instance, an electronic record in an old CDS used a specific colour for its chromatograms and accompanying text, and a replacement CDS can not replicate that colour, as it uses different colors to represent chromatographic data. In order to

ensure that a reviewer could correctly interpret the information, the guideline document proposes that a new electronic record is created to supplement the migrated electronic record, which explains the correlation between the old and new colour representations. While this solution would comply with Part 11, it would appear to be unwieldy and a potentially error-prone approach. A better approach would be to ensure that an accurate and complete representation of the electronic record can be migrated and archived along with the actual chromatographic data in its original format, which can be verified as secure at source. This constitutes a much simpler and secure method of maintaining migrated electronic records.

In Summary

Ensuring data integrity, security and traceability through CDS functionality at the acquisition stage can be a key factor in achieving compliance with Part 11. In recent years, most mature commercially available CDS can be configured to comply with Part 11 incorporating, as standard, features such as data security measures and functionality to enable electronic signatures. It is anticipated that draft guideline 00D-1539 will raise the bar on what constitutes compliance for the maintenance of electronic records for their whole retention period. Accordingly, the document is likely to have a similar effect on what regulated laboratories expect in terms of new CDS functionality.

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