Electronic Signatures: Systems or Applications?

R.D. McDowall, Ph.D.
McDowall Consulting, Bromley, Kent, UK

When we implement electronic signatures we focus on individual 21 CFR 11 technically compliant applications that automate a part of an overall process such as pharmaceutical manufacturing. The reason is that we tend to purchase individual applications designed and programmed by a vendor with expertise in a specific technical area of the overall process. Electronic signatures therefore tend to be implemented by each vendor in their own way, with their own interpretation and within their own application. The problem comes when applications need to be interfaced together and electronically signed electronic records are transferred from one application to another. We have no standards or FDA guidelines to help us.

Introduction

The publication of the Electronic Records and Electronic Signatures (21 CFR 11) Final Rule [Ref 1] in 1997 allowed the pharmaceutical industry to use electronic signatures for electronic records that are produced under the applicable FDA predicate rules. Implementation of electronic signature systems have been relatively slow, due in part to the unavailability of technically compliant applications and in part to a reluctance of pharmaceutical companies to embrace the regulation that they actually requested in 1990.

In a recent paper in this journal, some of the benefits of using electronic signatures were outlined [Ref 2] in an example based on a quality control analytical laboratory. This discussion was focussed on a single area and not the overall process of pharmaceutical manufacturing or drug development. The purpose of this paper is to discuss the implementation of electronic signatures within a process and not a single application.

The options for electronic signatures under 21 CFR 11 outlined in the regulation [Ref 1] are:

- Electronic Signature: unique combination of user identity and password
- Biometric
- Digital Signature

However, irrespective of the type of electronic signature implemented, the regulations apply to all.

Focus on Computer Applications

Understandably we have focussed initially on applications for the assessment of 21 CFR 11 non-compliances and implementation of compliant technical controls for the use of both electronic records and electronic signatures. The reason is that a single application is usually under the control of a single entity, for example either a pharmaceutical company's software department or a commercial vendor. The reason is that a single application usually has a single point of contact to discuss and ensure technical compliance with 21 CFR 11 requirements. Furthermore, a single application is usually within the confines of a single functional group within an organization. However, note that in the whole of 21 CFR 11, there is no mention of the word "application", rather "system" is used.

These are knee jerk solutions in the overall scheme of a more complex problem. In the author's opinion, more consideration needs to be given to the overall design of the use of electronic signatures within the whole pharmaceutical process to ensure that electronic records and electronic signatures are trustworthy and reliable throughout the whole process. This will be explored in more detail in this paper.

Paper and Hybrid System Environments

Consider a production environment where there is a manufacturing process where paper or hybrid records are produced according to 21 CFR 211 for current Good Manufacturing Practice (GMP). Allied with this are the Quality Control laboratory results for analysis and release of raw materials, in-process materials and finished goods.

Each record required for the batch release must be signed according to the requirements outlined in 21 CFR 211 such as [Ref 3]:

- § 211.186 Master Production and Control Records
- § 211.188 Batch Production and Control Records
- § 211.194 Laboratory Records

In this paper world the handwritten signature goes with the record. For example, if you photocopy the paper record then the records and the corresponding signatures are copied; and the copies are authorised as copies. As preamble comment 110 notes: "The Agency also notes that in the technical paper record, the signature remains bound to its corresponding record, regardless where the record may go".[1] This is an important consideration when we make the transition from a paper environment to an electronic one.

Record - Signature Linking

21 CFR 11 (§11.70) requires that electronic signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied or otherwise transferred to falsify an electronic record by ordinary means.[1]

This is simply applying the same principles to the electronic environment as are currently used to ensure trustworthy and reliable records in a paper one. Therefore if the requirement is for the signature to follow the record in the paper environment; surely the same is required for an electronic one?

21 CFR 11 Electronic Environment

When developing an integrated 21 CFR 11 compliant environment, where electronic signatures are applied to electronic records, it will be necessary to use individual technically compliant applications on an application by application basis. For example, applications that could be used to construct this electronic environment are:

- Enterprise Resource Planning (ERP) System
- Manufacturing Execution System (MES)
- Laboratory Information Management System (LIMS)
- Chromatography Data System (CDS)

These systems will be classified as closed, as these electronic records will be under control of the people who generate the records. The records will be signed in each system, as required under the predicate rule, but electronic laboratory and manufacturing data will be integrated to provide the electronic batch records to release a batch of product.

How will electronic records be integrated and combined in this electronic environment?

Implicit Non-Compliance?

When transferring data or information between systems, we only transfer what we actually require, for example, results from a chromatography data system to a LIMS or analytical release from a LIMS to an ERP system. Note that currently we only transfer the information required – no more, no less.

Now consider the question:

Are we breaking the 21 CFR 11 regulations if we transfer electronically signed electronic records (i.e. results) from one system to another WITHOUT the signature?

Remember that §11.70 requires that electronic records and electronic signature be linked so that they cannot be excised or copied by ordinary means. However, when we design links between different applications so that users just transfer signed results without the electronic signatures, does that mean that an organisation is breaking the law?

Think back to Preamble comment 110 and extrapolate to process to the electronic world. In the paper world the signature goes with the paper record; why then in the electronic world should not the electronic signature go with the electronic record? Same principle and the same end result are to have trustworthy and reliable records. There are many discussions and debates that we can have around this issue but, as written, the regulation states that the signature-record link should not be broken.

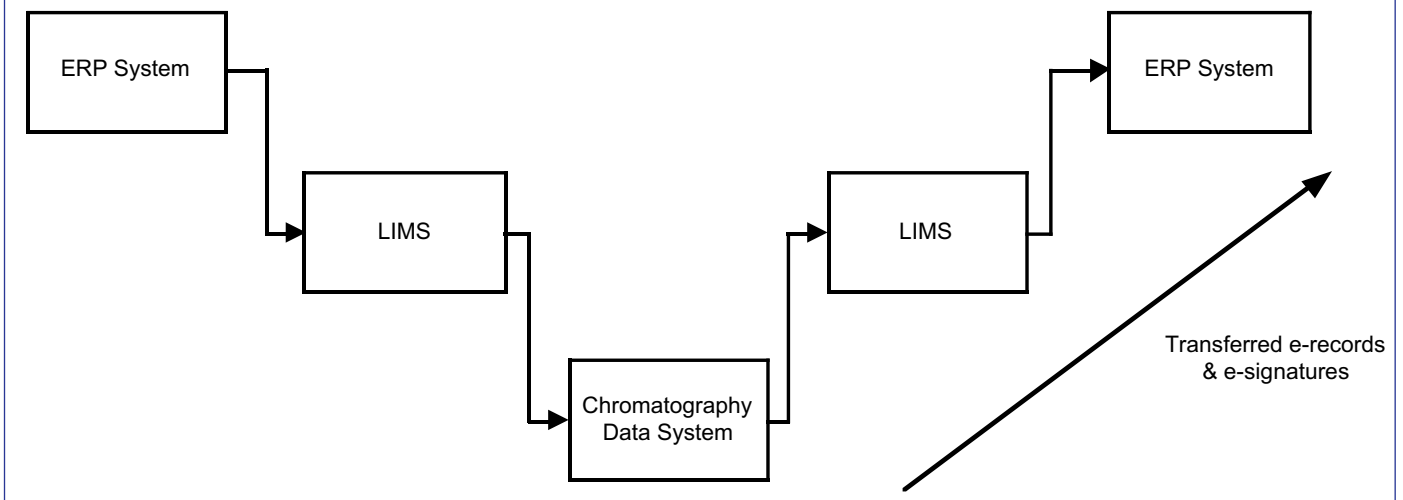
System versus Application?

As there are no applications that cover the whole of the R&D or manufacturing process, we need to build our electronic systems from individual application building blocks. Each of these applications will implement electronic signatures in a different way depending on the vendor's and their customer's interpretation of e-signatures. This view is application centric and inward looking; but understandable.

However, there is little or no consideration of the transfer of results with appended signatures between applications.

FIGURE 1

Integration of Electronic Record and Electronic Signature Systems



Consider the scenario in Figure 1, there is an electronic environment where there is an ERP system integrated with a LIMS within a laboratory and the LIMS is interfaced in turn with a chromatography data system (CDS). All three applications are technically compliant with the requirements of 21 CFR 11 and have the ability to sign records electronically and we will assume that signatures have been implemented in all three systems. Therefore, the process associated with the chromatographic analysis of raw materials, intermediates and finished products is automated and all records can be signed all through to the release of the batch.

The issue is, during a QA audit or inspection, the integrity of any signed electronic record may be investigated. If an analytical record is inspected in the ERP system, this may require a further check back into the LIMS or CDS to ensure the trustworthiness and integrity of the record. However, if the signed record were transferred to the ERP (or any other system), then this may alleviate the need for a further inspection or check.

Therefore do we need to consider standards for electronic signatures to ensure that they can be transferred to other systems effectively? If this is the case, perhaps we need to standardize on digital signatures rather than electronic signatures, even for closed systems to ensure that we can maintain the integrity of signed electronic records. Using this approach, providing that the appropriate administrative and procedural controls are in place, signed electronic records can be easily passed between systems whilst maintaining the integrity of the records more effectively than now. ■

References

1. 21 CFR 11, Electronic Records; Electronic Signatures, Final Rule, Federal Register, 62 (1997) 13430-13466,
2. R.D.McDowall, American Pharmaceutical Review, X (2001) xx-yy
3. 21 CFR 211, Current Good Manufacturing Practice Regulations for Finished Pharmaceutical Products, Federal Register, xx (199X) Pages

Dr. McDowall is a consultant specializing amongst others, with computerized system validation and electronic records and electronic signatures. Dr. McDowall has published many articles on these and other subjects. He received his undergraduate degree in Biochemistry from Newcastle University and received his Ph.D. in Toxicology from London Medical College.