Exploiting the Benefits of 21 CFR 11

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Much discussion has been focused on the costs and effort required by the pharmaceutical industry to become compliant with the requirements of 21 CFR 11 (Electronic Records and Electronic Signatures) regulation. The preamble to the final rule estimated that cost to industry for implementing the requirements of 21 CFR 11 would be "broadly cost neutral" [1], in marked contrast to the estimates from two companies who estimated that the cost for compliance to be in the range $130-150 million[2]. Most emphasis has been placed on the assessment of current (legacy) systems.

However, the purpose of this paper is to draw attention to the benefits that can be exploited from implementing a compliant system for both electronic records and electronic signatures. It develops the theme of an earlier paper of mine in American Pharmaceutical Review[3], that proposed when implementing a compliant system you should consider redesigning your existing processes to exploit the benefits that is possible under the scope of 21 CFR 11.

While many systems fall under the electronic record section of Part 11, many organizations are wary of implementing electronic signatures even when compliant solutions are available. Reasons for this are many and include the following:

- Fear of change in working practices
- Electronic signatures are unknown or should be avoided
- Comfort with using existing paper records and systems

In fact, implementation of electronic signatures is relatively simple provided there is a compliant solution available. This is in contrast with the problems faced with managing electronic records over the entire record retention period. This might include changes in file format, different archive media used over the time plus potential data migrations - as well as being able to replay the data.

To illustrate the benefits possible under 21 CFR 11, we will look in an analytical laboratory, specifically at the process for analysis samples using a chromatography data system (CDS). The scenario is based upon several laboratories and the author's experience.

When upgrading to a compliant system, take advantage of the significant business opportunity this presents and benefit from 21 CFR 11 and work electronically. Some of the aims should be to:

- Reduce process bottlenecks
- Design efficient handoffs and transfers between groups and systems
- Eliminate paper
- Reduce the number of systems and hence the overall validation burden
- Eliminate multiple manual entries into systems and paper
- Rationalize the electronic signature and electronic identification requirements to ensure compliance
- Saving time and personnel effect through the new process
- Design the process for consistency

After all, as the pharmaceutical industry asked for a regulation on electronic signatures in the first place, let's exploit the regulation and obtain the benefits that we originally wanted.

Map the Existing Process

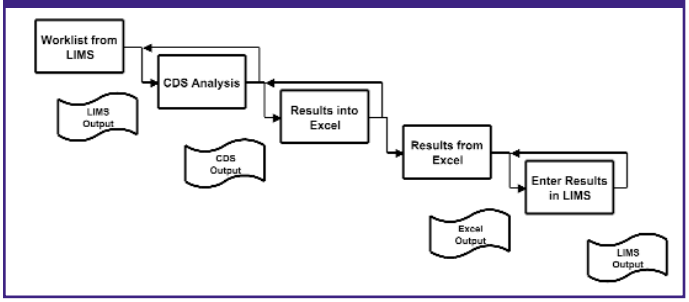
To exploit 21 CFR 11 benefits, the existing process is unlikely to be particularly efficient; many processes in the pharmaceutical industry have evolved over time and these are not usually designed. Only when a process is mapped will the users and process owner appreciate how inefficient and ineffective the process actually is. Therefore, before implementing a 21 CFR 11 compliant system and exploit the benefits of the regulation, the process needs to be mapped, understood, the bottlenecks identified, where are signatures (as opposed to identification) required and the process metrics measured (sample turnaround time, number of samples etc).

In this paper, we will look at a chromatography laboratory that has the following computerized systems that accompany a paper-based process:

- LIMS that is used for sample tracking and reporting results
- CDS for analysing data and measuring peak area
- Excel used for calculating results from the CDS such as system suitability tests criteria and analyte amounts

This scenario is typical in many organizations and as we walk through the process redesign you'll be able to see the benefits that can be obtained from 21 CFR 11.

Figure 1. Existing Chromatographic Analysis Process with Feedback Loops and Paper Printouts



The existing analytical process is shown in Figure 1; analysis of this process shows that there are five process steps with the following features:

- Mainly manual work with multiple data entries and transfers into the three applications (LIMS, CDS and Excel)
- Paper based approach to records management with handwritten signing
- Three potential rework loops due to transcription errors following the manual entry of data into the three systems
- Four printouts to manage plus any associated laboratory notebook entries
- Three individual system validations are required for the three applications
- Three hybrid systems with the associated problems of managing and synchronizing the electronic records and associated signed paper records
- Bottlenecks in the process that cause delays in the process

21 CFR 11 compliant chromatography data system and LIMS can be implemented either on the process outlined in Figure 1 or on a redesigned process. Excel can be made compliant with the use of add-ins such as DaCS (Wimmer Systems). However, given the high level of manual involvement in the process it is unlikely that significant business benefit will be obtained if the existing process is updated with Part 11 compliant software applications, as there is the inherent inefficiency of the current process. Therefore, the process should be examined to see where improvements could be made to take advantage of 21 CFR 11. We will explore some of the process redesign options to see which changes can be made.

Simplify and Redesign the Process - 1

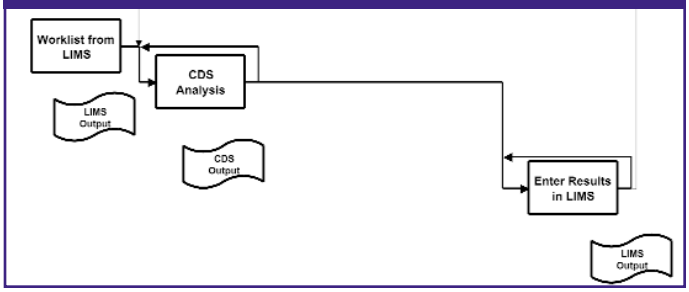
As a starting point for reviewing the process, assess if the calculations performed by Excel can be undertaken by the CDS. For example, the system suitability calculations that are performed in the spreadsheet can usually be performed in the CDS as these calculations are an integral part of the chromatographic process. Calculation of analyte amount or concentration is part of the usual functions of the CDS, so why do analysts use spreadsheets?

Custom and practice is a normal response: "we have always done it this way." The reason is that the spreadsheet is relatively easy to use and users can develop their own calculations, and this can be easier than learning to use the CDS functions. However, eliminating the spreadsheet and performing the calculations in the CDS will eliminate:

- One application (Excel)
- One hybrid system
- One rework loop
- One paper printout
- Manual transfer into Excel

The process is now redesigned as shown in Figure 2.

Figure 2. Redesigned Process After Eliminating Excel



One advantage is now apparent from the elimination of the spreadsheet; as the results are now all contained within a single system you can now utilize electronic signatures to sign-off and approve the final results. Here mapping the process will be very useful as you can highlight where in the current process are the approvals and identification on existing paper records. Again there is the issue of custom and practice; there is a tendency to sign virtually all records that are on paper. Review these and compare them against the signing requirements in the predicate rule places are all of these required? Ensure that the CDS can identify the individual making any changes to the electronic records and check that the electronic signatures in the new process are in the correct place and cover all appropriate records.

At the end of this phase of the process redesign, the CDS will be operating with compliance with the 21 CFR 11 with electronically signed records. However, the system is only standalone and to transfer the results to the LIMS, the results will need to be printed out and results entered manually into the LIMS. To improve the process further and obtain further business benefits, we need to consider interfacing the CDS with the LIMS.

Simplify and Redesign the Process - 2

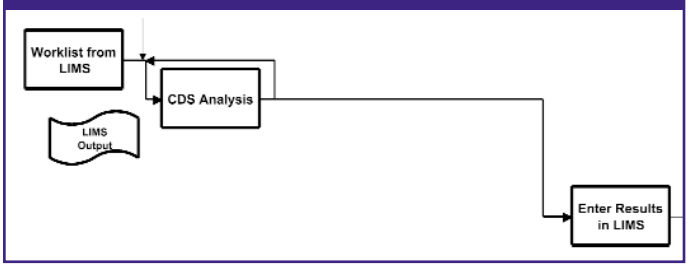
As outlined above, the next stage is to look at the interfacing of the CDS with the LIMS, this will be covered in two parts, firstly the unidirectional interface and then the bi-directional interfacing.

To speed up and improve the process, interface the two systems to transfer approved and electronically signed results from the CDS to LIMS automatically. Once this process is completed and validated, you can eliminate:

- One manual transfer & replace with a validated automated one
- Transcription error checking the manual entry
- Two printouts (one from the CDS and one from the LIMS)

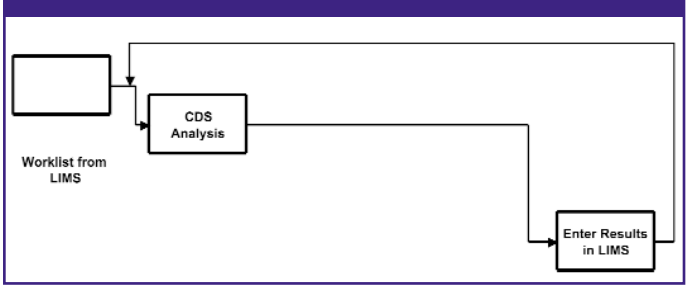
This redesign step will provide a rapid payback of the investment in the design and validation of this interface as manual input should be eliminated from the process. This process is shown in Figure 3.

Figure 3. Redesigned Process After Connecting the CDS to the LIMS for Unidirectional Results Transfer



The final stage of this process redesign is to complete the LIMS to CDS interfacing and allow the download of a work list from the LIMS to the CDS. This allows the CDS to import the file and incorporate it in the sequence file. This will save manual input of the order of the sample analysis and eliminate the final paper printout and the final process redesign is shown in Figure 4.

Figure 4. Paperless Process Utilising Bi-Directional Data Transfer Between the LIMS and CDS



Cost-Benefits of the Process Redesign

Process redesign is an essential tool in exploiting 21 CFR 11 as working electronically allows an organisation to obtain significant business benefits. Significant savings and time savings can be obtained if you take the time to stand back to map and review your process. Some of the savings that can be realised are based upon the following activities:

- Reduce number of applications to validate
- Eliminate manual involvement in the process e.g. tasks such as typing data into systems followed by manual transcription error system
- Eliminate tasks from the process to save overall time for process execution

To show the benefits of this approach, a case history of a process redesign with calculated business benefits will be presented in this journal.

Case Study Description

To illustrate this principle, I will examine a case study where electronic signatures were designed into the process. The application is a chromatography data system (CDS) installed in a pharmaceutical quality control laboratory where the system is used for both raw material and finished product analysis; there are approximately 50 users of the system. The current CDS version is not fully compliant with the technical requirements of 21 CFR 11 and is being upgraded to a new compliant version of the software. Before the implementation of the new version, the current process was mapped and analyzed to see if there were any opportunities for improvement and to make effective use of electronic signatures.

Please note that these are interim results as the system is not fully implemented yet, but the potential cost savings from this case study make a compelling business case for the implementation of electronic signatures. Further details will be published after the system has been validated and we can assess the impact of the redesigned process.

There is also a LIMS that is operational in some of the sections within the Laboratories. However, at the moment, there is a mixture of both lab notebooks and a LIMS being used.

The Current Process

The first task is to map the current process. This is relatively quick and the current laboratory high level process is shown in Figure 1. We can see that there are parallel electronic and paper activities when chromatographic analysis is undertaken. For example, when a chromatograph is set up, a paper record (Lab Book) needs to be updated and checked. When results are calculated, the report and chromatograms are printed out and the Lab Book is updated and checked again.

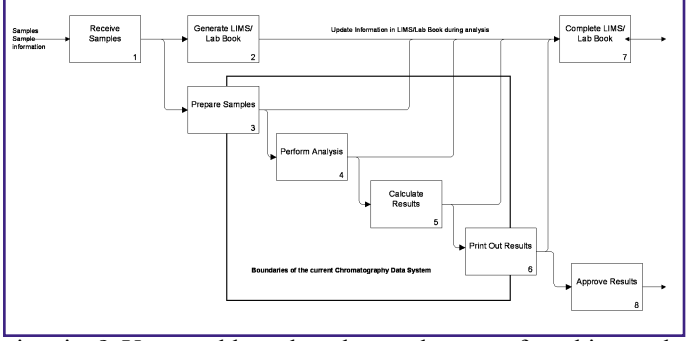
It is important to analyze the current process, for instance:

- What are the process metrics? For example, how many samples are analyzed and what are the turnaround times?
- Analyze the turnaround times: what are the reasons for fast and slow turnaround?

Answers to these questions will give you the information to start to improve the process and make it more effective and efficient.

The boundaries of the current version of the data system are also shown in Figure 5. In the current system, the approval of results occurs outside of the chromatography data system on paper. How could you implement electronic signatures in this

FIGURE 5. THE CURRENT PROCESS HIGHLIGHTING THE BOUNDARIES OF THE CURRENT VERSION OF THE CDS



situation? You would need to change the way of working to do this.

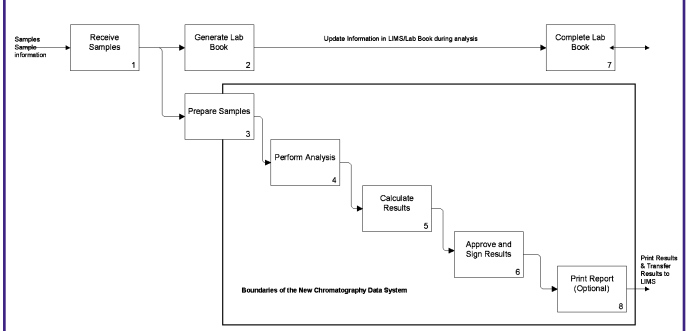
The Redesigned Process

Knowing the problems and improvement ideas from the analysis, the current process can be redesigned to exploit the use of electronic signatures. It is important at this stage to ensure that the new process is compliant and that the new version of the CDS can support the new process as well.

The redesigned process is shown in Figure 6, the main differences are:

- Elimination of the need to update the Lab Book for chromatographic analysis. This is a quick win that is estimated to save about 0.3-2.6 FTE (Full Time Equivalents or person years). This is independent of implementing electronic signatures in the CDS.
- Expanding the scope of the CDS. In effect, the approval of electronic records and calculated results takes place in the CDS and the printout is an option.
- Using the CDS to carry out all calculations rather than using a calculator or spreadsheet, this streamlines the whole process for calculating, reviewing and approving results.

FIGURE 6. THE REDESIGNED PROCESS HIGHLIGHTING THE EXTENDED BOUNDARIES OF THE NEW VERSION OF THE CDS



The benefits of the process redesign when the CDS is linked to the LIMS would be in the region of 6-12 FTE. This is a surprising benefit but enables more capacity to be generated with the current resources. As the LIMS/CDS link will not be implemented until later in 2002, the current estimate of savings is in the region of 0.5 – 3 FTE.■

References

1. 21 CFR 11, Electronic Records and Electronic Signatures Final Rule, Federal Register
2. Pink Sheet December 1999, FDA Reports Washington DC p1.
3. R.D.McDowall, American Pharmaceutical Review September 2000

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 the University of Newcastle upon Tyne and his PhD in Forensic Toxicology from the University of London (London Hospital Medical College).