How To Guide

How To Future Proof Your Laboratory Informatics Environment

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The purpose of this guide is to discuss ways to ensure that laboratory computerized systems meet both business needs and compliance with relevant standards or regulations. We'll also explore how these systems can be designed to operate for a long time without the need for changing a business process. As the World Health Organization's (WHO) good records and data management practices notes in section 5.6:

> *A data management program … is expected to leverage existing technologies to their full potential. This in turn will* ***streamline data processes*** *in a manner that not only* ***improves data management but also the business process efficiency and effectiveness****, thereby reducing costs and facilitating continual improvement.*[1]

This explicitly requires process understanding and simplification and implicitly requires automation or digitization to achieve business efficacy and effectiveness.

Both the WHO and PIC/S data integrity guidances go further and recommend that hybrid systems (computerized systems generating electronic records with signed paper printouts) are not encouraged and should be replaced at the earliest opportunity.[1,2]

Furthermore, the US Food and Drug Administration (FDA) is forcing some laboratories to automate via warning letter citations:

- Stason Pharmaceutical and Tender Corporation, issued in July 2020, were both required to interface instruments such as balances and pH meters to a LIMS network[3,4]
- BBC Group, cited in August 2021, bought analytical instruments that had the capability to store electronic records but the laboratory did not use it, relying instead on paper records[5]

These three warning letters have been reviewed in more detail by the author.[6,7]

The bottom line is that any laboratory in the future must implement electronic workflows that include elimination of paper printouts and the use of electronic signatures. Your laboratory will either get there voluntarily or by regulatory compulsion. To realize electronic working that ensures both compliance and meets business needs, you need a plan for automation.

Laboratory automation strategy

It is vital that a laboratory has a strategy that plans projects for automation. Think of a jigsaw puzzle as an analogy, the pieces are the elements of the automation strategy and the picture on the box is the plan.

The first pre-requisite for an automation strategy is a robust and resilient IT infrastructure. If all laboratory records are electronic then the IT platform must be available, work reliably and must ensure that backup, disaster recovery and business continuity are current and tested. However, we will focus here on informatics applications with the aim of automating laboratory processes.

There are several processes that occur in any regulated laboratory some of which are listed below:

- Sampling and sample management
- Specifications management
- Reference standards management and use
- Instrument calibration and qualification and software validation
- Methods development and validation
- Sample preparation and analysis
- Stability testing
- Data management and reporting
- Deviation management and laboratory investigations

The diversity and interdependencies of these processes is why an overall strategy is needed as a single application cannot automate them all.

Informatics components and some factors to consider

The concept to consider is the LIMS environment. This is not a single application but a combination of best of breed applications to meet business and regulatory compliance needs. The pieces of the jigsaw to define their automation strategy and their integration with the rest of the organization are:

- Instrument Data Systems e.g., Chromatography Data Systems (CDS)
- Laboratory Execution Systems (LES) and Electronic Laboratory Notebooks (ELN)
- Laboratory Information Management Systems (LIMS)
- Scientific Data Management Systems (SDMS)
- Enterprise Resource Planning (ERP) systems

Some factors to consider when developing the automation strategy:

All laboratories are the same...

All regulated laboratories have the same function to analyze samples and report results for either product development or release. A naïve assumption would be that one size fits all informatics solutions fit all would be applicable. This is wrong.

... Except for the differences

There can be many differences between laboratories when you get into the detail and these are a result of management approaches, type of analysis undertaken, previous investment to keep current,[8,9] compliance history, etc. The differences between how a manager thinks a laboratory works and the

reality can result in some very expensive automation mistakes. Knowing the details of a process is key as we shall see later.

Company ego

Some companies have a view that there are only two ways of working: our way and the wrong way. This can commit a laboratory to extensive application configuration or customization which is slow and expensive to implement. A better way is to take the basic workflow of an application and fit the laboratory to this and make as few changes as possible to meet business and regulatory requirements as we shall see later.

What applications do you have and how well are they used?

The current computerized systems should be assessed. How well are they used and can their use be improved? For example, is a chromatography data system just being used to measure peak areas, with spreadsheets then used to calculate sample results? Incorporating the calculations in the CDS eliminates the spreadsheets and transcription checking and is faster.

Application convergence (or expansion)

In the past, several systems were required to automate a laboratory, but applications are now converging or expanding e.g., LIMS have LES functionality and vice versa. This means that fewer applications could be required – reducing interfaces and validation costs.

Experience and maturity with informatics

A crucial factor to consider for any automation strategy is how successful the organization is in implementing informatics applications. Are projects:

1. On time and on budget?
2. Liable to suffer from scope creep and subsequent delays?
3. Unable to meet deadlines and budgets?
4. Always able to deliver business benefits?

This will determine how adventurous or cautious any automation strategy will be.

Regardless of the answers to the questions above, it is critical to ensure that the first project is a success; it must deliver both business benefits as well as ensure data integrity and compliance.

Some further considerations for the automation strategy are:

- **Specification management:** Where will product specifications be stored and managed? The location might be an ERP, LIMS or another application. How will the specifications be input: automatically from a specification database or manually entered by the laboratory?
- **Management support:** This is a critical factor as senior management support and resources are needed for an automation strategy to proceed. Management support, both formally and informally, is essential to influence and persuade staff to support the overall automation program.
- **Small instrument interfacing:** There is a debate whether smaller instruments such as analytical balances, pH meters, etc. should be interfaced to e.g., instrument data system, LES or LIMS. The key requirement is to remove paper from the process and to capture data electronically at the point of origin. To do this the small instruments should be integrated with the process flow.

- **Do you need a LIMS when you have an ERP?:** In some organizations with an ERP, the quality module is used instead of a LIMS, this can provide a close link with specifications and production. There can be limitations with instrument interfacing and automation of some peripheral processes unless extensive customization is undertaken. An alternative could be to interface the ERP to an LES with sample management, interfacing to analytical instruments and electronic workflows.

From these considerations, the automation strategy is built with several individual projects for automating the laboratory. However, the key to success of all these projects is process understanding and redesign as highlighted in the WHO quotation[1] at the start of this article.

Process improvement for effective informatics implementation

The key to ensuring that any informatics solution is long lasting is process understanding. This is achieved by mapping your current and future ways of working in two workshops.

- A high-level process map should contain between 8 and 12 main activities, each of which can be broken down further into more detail.
  - For most laboratory processes, two levels of mapping are usually sufficient
  - The main exception is where two systems are interfaced and there may need to be two process levels for each one to understand the detail of the interactions

- When mapping is finished, the data vulnerabilities, bottlenecks and problems with the process should be identified and documented against an activity
- Lastly, the attendees should be asked to give their ideas for process improvement

Mapping can be undertaken by using sticky notes, either on a white board or large paper sheets. When the maps are finished, the sticky notes should be used as inputs to an application such as Visio. It is unlikely that you will get the mapping right first time, so it is important that the process maps are circulated to staff to review and comment on before the second workshop.

- The current process maps are reviewed, any mistakes or omissions identified and the maps updated where necessary
- The best improvement ideas are then used to change and streamline the process to eliminate data vulnerabilities, paper printouts, spreadsheets and bottlenecks
- The aim is to have an efficient and compliant process that can be implemented in an informatics solution as part of the LIMS environment

The redesigned process is then used as a basis for implementation of an informatics application. There may be features in the software that improve the redesigned process further than anticipated and these should be used.

Prototyping is a powerful way of checking that the automated process works and is compliant; prototypes should be evaluated by as wide a range of users as is feasible, with their feedback incorporated as modifications to the electronic process. From a validation perspective, the prototyping can be undocumented, but the final configuration of the application must be documented.

This can be seen a case study example of a current and redesigned process in the next two sections.

An analytical process – 1: What is your current process?

The current process map of a chromatographic analysis is shown in Figure 1 which depicts the following disaster zone:

- Weighing of the reference standard and sample aliquots for analysis with associated balance printouts
- Determination of the water content of the reference standard with the printout from the Karl Fischer titrator
- Preparation of the samples for analysis using volumetric glassware and transfer into injection vials for chromatographic analysis. This work is recorded manually either in a laboratory notebook or analytical batch record
- Analysis by chromatography and, following interpretation of the chromatograms, printout of the chromatograms
- Input of peak areas, reference standard water content, sample weights, any dilution factors and purities into a spreadsheet (hopefully validated) for calculation of aliquot results and the reportable result
- The analytical report is generated in a word processor and signed by the analysis and supervisor

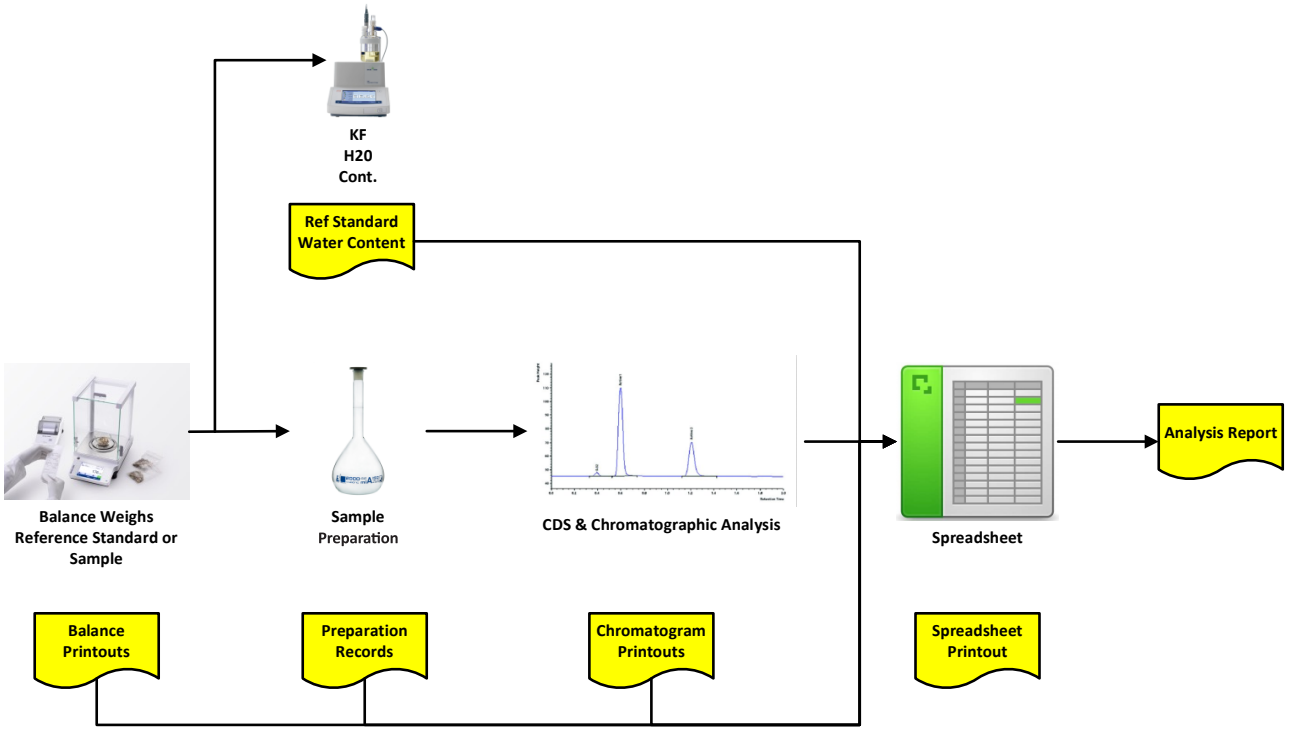

Figure 1: High level map of a current process.

This is a hybrid system nightmare with multiple paper and electronic records that are difficult to coordinate, especially for second-person review. There are multiple manual data entries into the CDS and into spreadsheets. From a business efficiency perspective, this process is deathly slow.

This process is ripe for process redesign and the implementation of electronic working to improve laboratory efficiency, transparency and compliance.

An analytical procedure – 2: The redesigned process

After following the process redesign framework described earlier, the process is redesigned to improve efficiency, eliminate paper, use electronic signatures and ensure data integrity. The new process is shown in Figure 2; this is not the only solution that is possible but is used to illustrate the process mapping and redesign approach.

The main process improvements made are:

- Implementation of an informatics application such as a LIMS, ELN or LES to automate the overall process, interface instruments and collate sample and result data. This allows spreadsheet calculations to be incorporated into either the informatics application or the CDS and eliminate the spreadsheet and several printouts.
- This system is interfaced to the:
  - Analytical balance to ensure data capture at source directly to the informatics application of sample and reference standard weights
  - Karl Fischer titrator to collect the result from the instrument and automatically calculate the water content of the reference standard using the weight from the balance
  - CDS, where sample and standard weights, sample dilution factors and reference standard water content are transferred electronically from the informatics application to the CDS along with sample information for the chromatographic analysis
- Sample preparation is automated by incorporating the instructions into a LES process flow and documenting steps via a mobile device by typing or by voice input. Recently, QR-coded glassware has become available so that an individual item of volumetric glassware can be identified. Direct data entry to a computerized system ensures a contemporaneous record.
- The CDS now has all the information to perform the analysis, after interpretation of the chromatograms, the reportable result is calculated and transferred to the informatics application.
- The informatics application can then generate the report automatically which can be electronically signed by the analyst and reviewer.

An alternative approach could be to use an instrument data system from the balance and KF titrator supplier that could be used to control these, which in turn is interfaced to the other informatics application used in Figure 2.

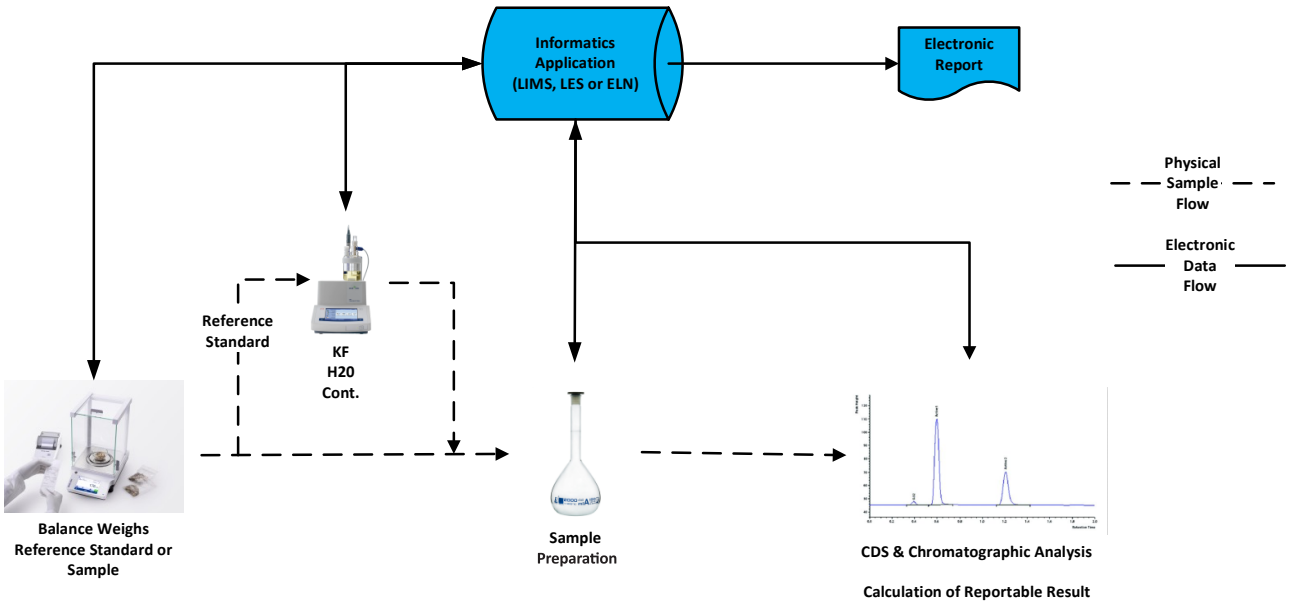

Figure 2: The Redesigned Electronic Process

Regardless of approach, the entire process is now electronic, which allows review of data either on site or remotely; the latter is important in light of working practices with the pandemic.

Summary

For successful digitization of a laboratory, an automation strategy is essential. It records the systems you have now, whether changes can be made to their operation or if they have to be replaced or upgraded. The strategy should define a number of projects and their order of execution. Regular review and update of the strategy is essential in light of changes in regulations, new informatics software or business requirements.

The key to success when implementing any informatics application is process understanding. Mapping the current process enables objective decisions to redesign the process and improve business efficiency, regulatory compliance and ensure data integrity. If this is done correctly the resulting automated process will last a long time and future proof your informatics investment.

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