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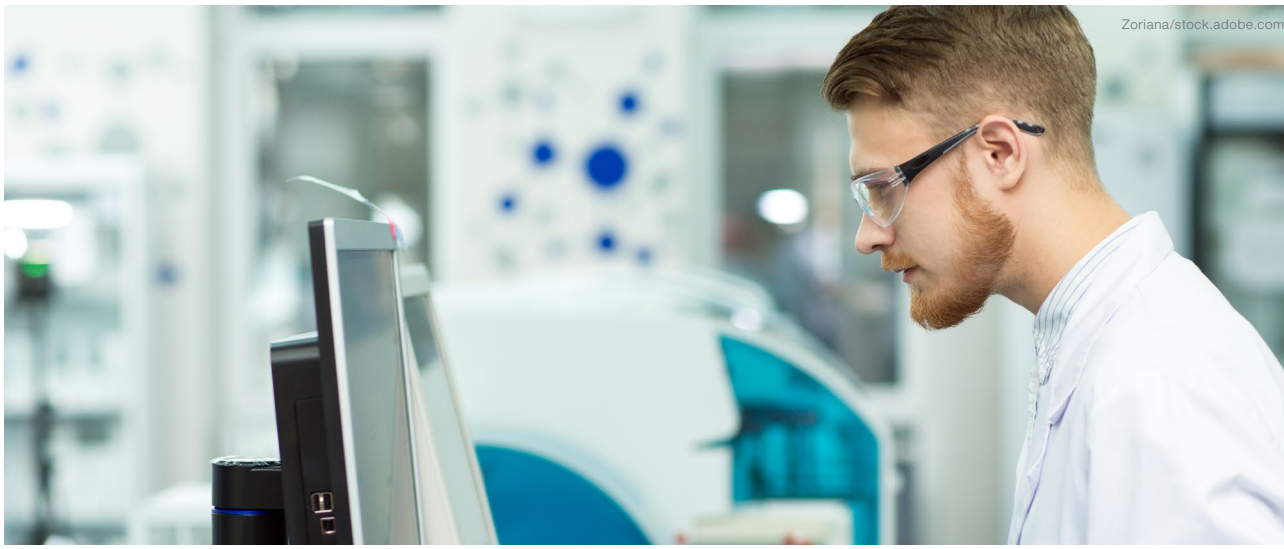


A Practical Approach to Building an Electronic Laboratory, Part 1

R D McDowall and Nicolas Louvet

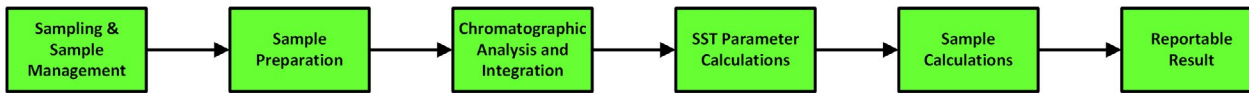
A review of where are we now in terms of building an electronic laboratory.

Introduction

To discuss a practical approach to building an electronic laboratory, we first need to understand what the current situation is in many laboratories and what potential problems there are to prevent working electronically. To achieve this, we will review the following:

- The analytical process from sample management to generating the reportable result.
- Understanding and balancing the cost of compliance versus the cost of non-compliance.
- Why it is important to map and understand your processes.
- Review the spectrum laboratory informatics applications.
- Discuss the journey to digital.
- Discuss *quo vadis* laboratory automation as a link to the second part of this journey.

FIGURE 1: The analytical process from sampling to reportable result.



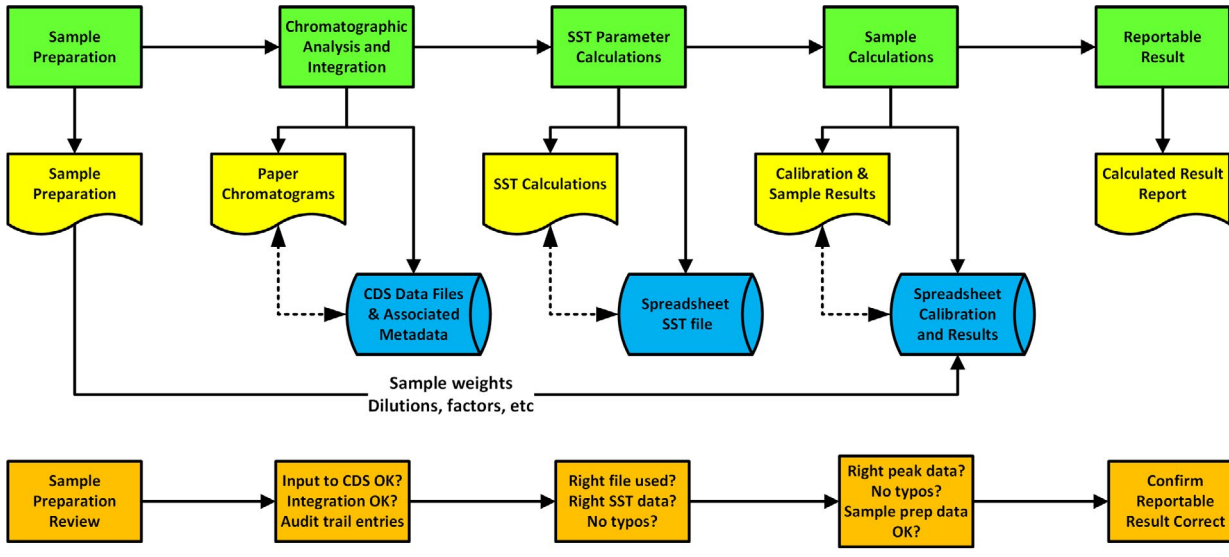
We will start with considering the analytical process from sample management to the reportable result.

The Analytical Process

The analytical process shown in FIGURE 1 describes the high-level workflow from taking a representative sample through analysis to generating a reportable result. In this discussion, we will focus on the laboratory tasks from sample preparation to reporting. The whole purpose of analysis, apart from having some fun playing with instrumentation, is to generate information to make a decision. The decision taken will depend upon where the laboratory sits within the pharmaceutical research, development and manufacturing spectrum. For example, if the laboratory is involved with analytical development in R&D, data for product submission to regulatory agencies will be generated. In contrast, a quality control laboratory will use the information generated from analysis to decide whether to release a batch or not, or if a product is within predefined stability limits.

To make a decision, it is important that you understand how the analytical data are generated. This is because any analytical result requires the underlying data to have the data integrity attributes (e.g., ALCOA+

FIGURE 2: An analytical process involving hybrid records.



criteria) to trust the numbers generated and the quality criteria (e.g., accuracy, timeliness) to make the decision. As the analysis progresses through the process flow shown in FIGURE 1, from left to right, you gain more information from the sample until the reportable result is generated.

Processes Can Evolve Over Time

An important understanding of where we are now is the assessment of a laboratory's current processes, which have typically evolved over time rather than having been designed to be efficient and effective. An example of a current chromatographic process map is shown in FIGURE 2, which, unfortunately, is based upon a real case study. This is an example from two laboratories where the processes have been merged together. In FIGURE 2, we have the following:

- Green represents the process flow from sample preparation to reportable result. Note that no rework loops (e.g., due to mistakes or laboratory investigations) are shown to simplify the figure.
- Yellow and blue are the paper and electronic records, respectively, produced during sample preparation, by the chromatography data system and the two spreadsheets used in the process. One spreadsheet is used to calculate system suitability test (SST) parameters and a second is used to calculate the reportable result by manual entry of peak areas. The CDS is now the world's most expensive electronic ruler as it only calculates peak areas.

Orange shows the tasks performed by the second person reviewer to confirm that the work and calculations have been carried out correctly, the records are complete, and that the analysis is accurate. The instrument logbook is not shown in this figure.

Let us dissect the process in FIGURE 2 together with the data and records generated:

- Sample preparation is manual and generates multiple data elements written on paper such as batch number, sample identity, sample weights, reference standard used together with weight, purity, water content, and so forth. These data are used later in the process and must be entered manually into the CDS as well as each of the spreadsheets.
- Three computerized systems are involved in the process: the CDS and two spreadsheets (yes, a spreadsheet is a computerized system!).
- The computerized systems are all hybrid: signed paper printouts linked either to the underlying CDS contextual metadata including relevant audit trail entries or the spreadsheet files.
- There is manual data entry throughout the process. The typing skills of all analysts are excellent, and they never, ever make a transcription error, do they?
- One spreadsheet is used to calculate SST parameters. However, these parameters can be calculated automatically by the CDS without the pain of printing peak areas, manual entry of them into the spreadsheet, and then printing the results.

This process, as you can see, is poor but that is the calm before the storm. The storm awaits the second person reviewer.

Second Person Review

We now come to the poor person who is tasked with the second person review shown at the bottom of FIGURE 2. There are multiple transcription error checks throughout the process flow due to multiple manual data entries. This is a very painstaking and tedious task requiring much concentration and cross-checking between paper records and electronic data by an experienced analyst. This is a very time-consuming activity. When you see a process like this, you might ask yourself, "Why has this laboratory used a spreadsheet for calculation of system suitability test results when the chromatography data system does these calculations automatically, and for free?"

As we go into more detail, the complexity of the second person review becomes apparent such as:

- Is the sample preparation paperwork correct and complete?
- Are all manual entries correctly entered into the CDS from sample request and sample receipt?
- Has the correct instrument been used?
- Have the correct instrument, acquisition, and processing files been used?
- Are the date and time stamps of the CDS data files consistent?
- Is the peak shape consistent throughout the run?
- Are the peaks correctly integrated throughout the run?
- Is manual integration allowed and applied consistently?
- Have audit trail entries been reviewed?
- Have the right calculations been performed, and has rounding been correctly applied?
- Checks for any falsification and testing into compliance?
- Hybrid CDS printout matches the electronic records?
- Peak areas input correctly into the SST spreadsheet?
- Peak areas input into the results calculation spreadsheet?
- Hybrid spreadsheet printouts match the electronic files?
- All printouts correctly initialed/signed and dated?

This is due to the analytical process having evolved and not being designed. Contributory factors may also be not knowing the functions of the CDS and a failure of management to invest in training for the data system or automation of the process. It will not be a surprise that the review can take longer than the analysis itself.

The Hybrid Nightmare

Hybrid systems are the worst possible situation you could be in from a data integrity perspective. Hybrid systems are a data integrity nightmare. The WHO Records and Good Data Management guidance document in Appendix 1 under Attributable states:

- *Hybrid systems are not recommended*
- *Hybrid systems should be replaced at the earliest opportunity* (1).

This is about as close as any regulatory authority will get to saying not to use hybrid systems as there are two incompatible record formats to manage. If you update the e-records, you must print and sign another set of paper printouts, but how can you reconcile the electronic records with the first and second sets? The two incompatible media sets must remain synchronized throughout the record retention period. This is a nightmare. The best advice is get rid of paper and work electronically.

Spreadsheets Slow Down a Process

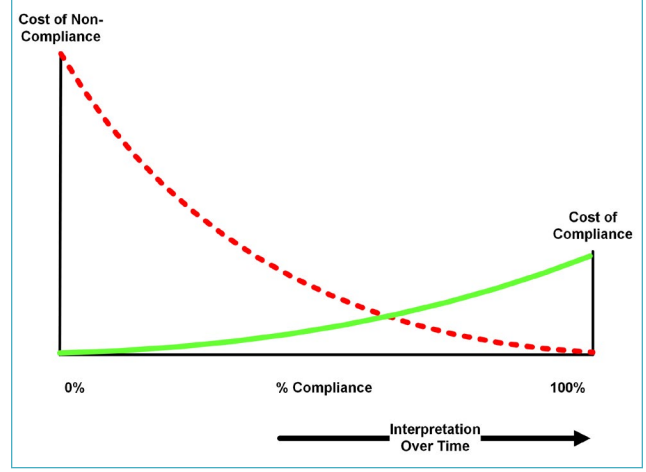
A spreadsheet is a computerized system as well as a hybrid system. Why are spreadsheets used when there is manual data entry and subsequent transcription error checking? The problem is, when you boot up your workstation, the first thing you'll see is the little icon that says Excel, which like a siren call to the gullible. Instead of reading the CDS help file and working out how to keep things within an informatics application and working electronically, analysts take the easy spreadsheet option with little thought of the consequences.

Understanding the Costs of Compliance and Non-Compliance

Risk management is one of the requirements for the pharmaceutical industry following the publication of the FDA's GMPs for the 21st Century (2) and ICH Q9 on Quality Risk Management (3). How much work is required in a regulated laboratory is dependent on a justified and documented risk assessment that must also be scientifically sound. This discussion can be summarized as the balance between non-compliance versus the cost of compliance. Each laboratory makes the decision along a spectrum from doing nothing to doing everything possible and this determines how much regulatory and business risk a company wishes to mitigate or carry as well as how much money the company wishes to spend.

The left-hand vertical axis of FIGURE 3 is the cost of non-compliance and the right-hand axis the cost of compliance. You will note that the cost of non-compliance axis is much bigger than the cost of compliance axis. One viewpoint is that one axis is logarithmic and the other is linear; Guess which one is linear. This is one of the balances you must consider. An alternative view

FIGURE 3: Understanding the costs of compliance and non-compliance (4, 5).



of the axes is that the right-hand side shows the cost of doing it right the first time and the left-hand side is the cost of getting caught. Fixing a regulatory problem that has been identified in a warning letter is always more expensive than doing the job right the first time or finding a problem and fixing it yourself. If any reader is in doubt about the cost of non-compliance for data integrity violations, read the consent decree for Ranbaxy (6), where the cost of non-compliance can be quantified as hundreds of millions of dollars.

In FIGURE 3, the horizontal axis is the percentage of compliance from 0% to 100%. The only fixed points are at the ends of the scale where 0% is where no control of the process or system and 100% is where anything that can be compliant is compliant. In between is a relative scale of compliance. The major point to note is that this scale is not fixed but moves as indicated by the arrow at the bottom of the figure. But the direction of movement is only one way and that is to the right! To understand this point, consider the situation with data integrity. The FDA GMP regulations have changed little since 1978 and have always contained data integrity requirements. However, since the Able Laboratories fraud case in 2005 (7) and discovery of industrial-scale data falsification and poor data management practices, we have seen a tightening of interpretation by regulatory authorities and the issue of many regulatory guidance documents (1, 8-12).

Citation one of the Able Laboratories 483 (7) states that the quality unit failed to review audit trail entries. In the FDA GMP regulations, even with the 2008 update (13), there is no mention anywhere of audit trail review. Since 2005, the regulatory expectation—and this has been reinforced by the Preapproval Inspection Compliance Program Guide (14, 15) and the 2018 FDA's Data Integrity Guidance (12)—is they expect laboratories to review audit trail entries. What you are seeing is a shift in percentage compliance to the right as shown in FIGURE 3.

Same regulations, more stringent interpretation. The reason for this shift is the *c* in cGMP.

Understanding *Current* in cGMP

To understand what *current* in cGMP means, we have to go back to the future and look at the Federal Register from September 29, 1978, the actual publication of 21 CFR 211 (16). In preamble comment 17 to the regulation, you will find the meaning of the word as intended by the FDA:

> *… a misunderstanding regarding the use of the word "current." …*
>
> *Congress intended that the phrase itself have a unique meaning and that the good manufacturing practice regulations represent sound current methods, facilities and controls for the production of drugs to assure safety…*
>
> *Although the practices must be "current" in the industry, they need not be widely prevalent. Congress did not require that a majority or any percentage of manufacturers*

> *already be following the proposed mandated practices, as long as it was a current good manufacturing practice in the industry, i.e. that it had been shown to be both feasible and valuable in assuring drug quality (16)*

There is an equivalent requirement in European Union Directive 2001/83/EC on Medicinal Products for Human Use. Article 23, §1 requires an authorization holder to take account of scientific and technical progress and enable the medicinal product to be manufactured and checked by means generally accepted scientific methods:

> *After a marketing authorisation has been granted, the marketing authorisation holder shall, in respect of the methods of manufacture and control provided for in Article 8(3)(d) and (h), take account of scientific and technical progress and introduce any changes that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods (17).*

In practice, what this means is what you did a few years ago is now sliding down to the left as the compliance interpretation moves to the right in FIGURE 3. Doing nothing results in a laboratory carrying more regulatory risk. If in doubt, read the Tender Corporation and the Stason Pharmaceutical FDA warning letters from July 2020 (18, 19) and the interpretation of them here (5). The key citation to both companies was:

> *Technological improvements to increase the integration of data generated through electronic systems from standalone equipment (e.g., balances, pH meters, water content testing) into the LIMS network.*

Both companies had extensive remediation mandated by FDA and both were required to implement improvements to increase the integration of data generated through electronic systems from standalone equipment (i.e., you've got to integrate your instruments to a LIMS or an ELN or a laboratory execution system). This is the *current* in cGMP in action.

However, spending money can be an anathema to management that believes it costs too much money to improve the laboratory. However, if you have several non-compliances, surprisingly, money flows like water over Niagara Falls. Look at the left side at FIGURE 3; it will cost you a lot more than if you were already on your journey toward the digital laboratory.

The advice is that a laboratory should have business needs pulling process improvement rather than the regulatory boot is pushing you down this road. It is better to present, "This is what we're doing" to a regulator, rather than the inspector saying, "Hang on, this is the same thing I saw last time and the time before that. You haven't evolved." Never assume that what was good enough at the last inspection will be good enough for this one. Issues around lack of laboratory data integrity will force you to go down the road of automation sooner rather than later.

Laboratory Informatics Applications

If we are going to automate, we need to look at some of the laboratory informatics applications available to automate processes in a regulated laboratory.

- Laboratory Information Management System (LIMS) for automating sample management, sample analysis, collation of results, and reporting all results for each sample.
- Electronic Laboratory Notebooks (ELN) intended for flexibility for automating R&D experiments with instrument connection to acquire and process data.
- Laboratory Execution System (LES) intended to automate manual analytical procedures with instrument interfacing. LES are intended for more rigorous procedures typically in a Quality Control environment.
- Instrument Data System (IDS) (e.g., chromatography data system [CDS]) for controlling instruments as well as acquiring, processing, storing, and reporting results of a test.
- Analytical Instruments for analyzing samples. These must be purchased with the ability to interface with the aforementioned informatics applications. Standalone instruments are not fit for purpose in a regulated laboratory.

There are three basic principles for automating a laboratory (20):

1. **Data Acquisition at Source**
   Capture data from analytical instruments directly into informatics solutions, never print.
2. **Never Retype Data**
   Once captured electronically, data must never be printed or manually entered into another computerized system
3. **Know Where the Data Will Go**
   To ensure data can be retrieved quickly in case of an audit, inspection, or complaint, it may be necessary to define file naming conventions. This may take time to organize, but it is better to work these out and even prototype them before implementation.

To implement these principles, we must consider starting from the analytical instruments and the various analytical processes. What types of data are acquired (e.g., text or observations such as odor or color), point values either singly or in sequences (e.g., pH meters and analytical balances), and more complex data (e.g., UV, IR or MS spectra, chromatography data)? These must be assessed and interfaced to networked rather than standalone data systems. Avoid a standalone system wherever possible.

To ensure and enforce data integrity and regulatory compliance, there should be technical controls enabled in the informatics solutions. One decision that must be considered is which informatics application are we going to use to automate processes?

- Are we going to use an LES?
- Are we going to use a LIMS?

- Are we going to use an electronic lab notebook?

You must be aware of application convergence. If we go back a decade or two, a laboratory would buy several applications and interface them together such as LIMS for sample management and reporting, LES for automating sample preparation talks, and an instrument data system such as a CDS. Each one does the job. However, over time LIMS start to get lab execution functions, electronic lab notebooks integrate and interface with instrument data systems, et cetera. It is important to be aware of what's happening in the marketplace so that you choose a system that will enable you to do possibly two or three things. Instead of buying different applications, try to purchase one to automate multiple tasks. Try to find a system that will run off the same database and be able to acquire data from instruments as well as automate laboratory processes.

This will enable you to meet the three automation principles and reduce paper.

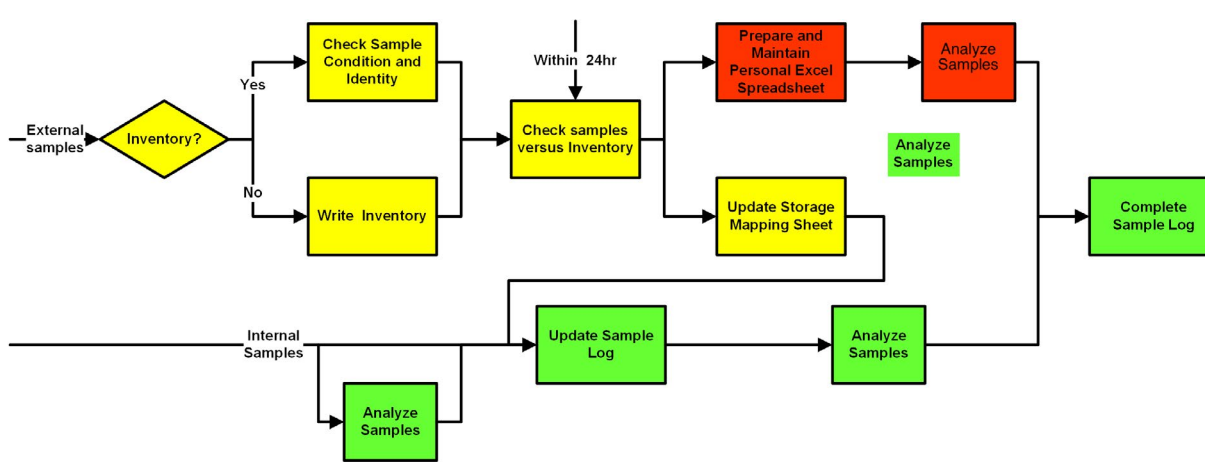
The key requirement before starting this journey is to map and understand your current processes. FIGURE 2 gave you a taste of a poor process but at a high level, however, to understand why process mapping is important before implementing an informatics application we need to go into more detail.

Map and Understand Your Current Process

The aim is to design laboratory processes to make them simpler, efficient, and effective—before implementing any informatics application. A case study example of a current process is shown in FIGURE 4. Ask yourself the question: How would you automate this mess? Let us examine the process:

- There are two entry points into the activity as external samples (in yellow)

FIGURE 4: A case study example of a sample management process.



are treated differently from internal samples (in green).
- The requirement for checking external samples versus inventory within 24 hours was instigated by the head of the department when samples went missing after delivery and the head was publicly admonished for this. The mandatory check was the outcome to save public humiliation in the future.
- There are branches depending if there is sample inventory or not.
- There is an undocumented process (shown in red) that one person uses as it is easier than the processes described in department SOPs.

If this process was automated, how would you implement it, validate it, and train the analysts? You cannot automate a mess. Any process must be redesigned before automating it to:

- Make it simpler and more consistent to operate
- Eliminate paper records as much as possible
- Be enforced technically by the software to minimize the risk of doing a task differently
- Ideally, a single set of activities will be applicable to all samples, regardless of their origin.
- Overcome big company ego (e.g., There are only two ways to do things: our way and the wrong way.)

In a current process, you must identify the bottlenecks or pinch points, then understand the reason for each one. Usually, this is due to a problem earlier in a process, which if resolved, eliminates the bottleneck. Reiterating our advice: mapping and redesigning your processes is essential before any informatics implementation. This results in the redesigned process for sample management shown in FIGURE 5, which has the following advantages:

- A single simplified process, which is easier to implement within an informatics application
- It is much easier to validate as there is only one process not three
- Simpler and easier to train users: they only work in one way

So far, mapping the current process and redesign has only been conducted on paper. We now need to see how it is translated into software and to look at the spectrum of software applications that we could use.

FIGURE 5: The redesigned and simplified sample management process.

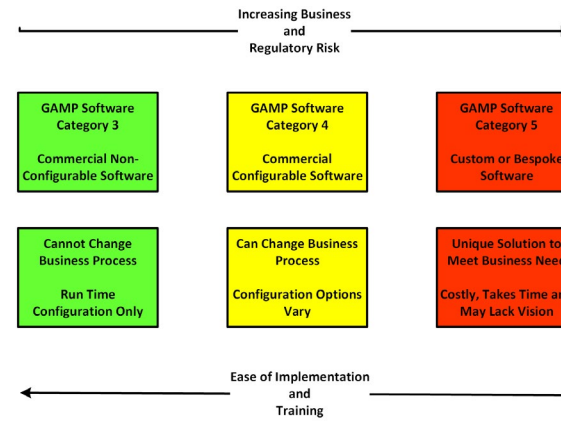
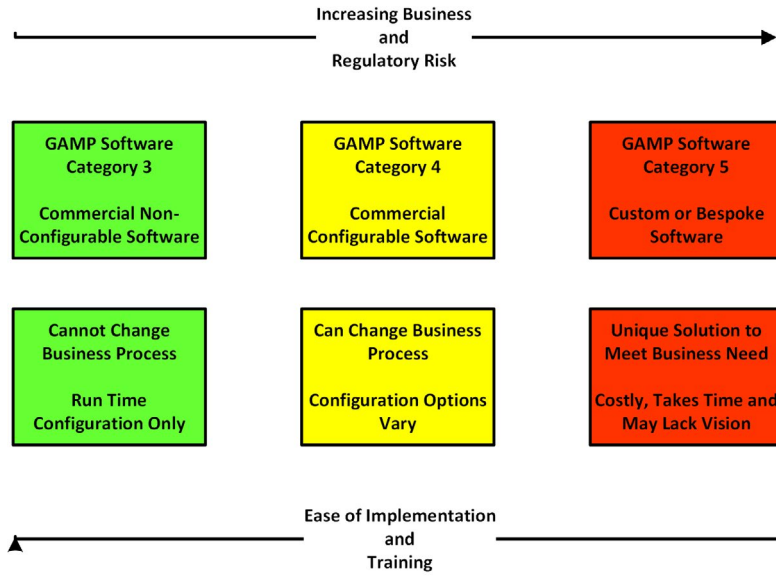


FIGURE 6: Spectrum of software applications according to GAMP 5 (21).



Automating the Process: Impact of GAMP Software Categories

The spectrum of applications is best classified using the categories presented in GAMP Guide version 5 (GAMP 5) (21). In Appendix M4, there is a classification of software categories and risk. For application software that can be used for automating laboratory processes, there are the following (see FIGURE 6):

- **GAMP Software Category 3 (green): Commercially available, non-configurable product.**
  You cannot change the business process being automated as it is fixed. You may do run time configuration (e.g., configuring reports, defining user access privileges), but the process it automates cannot be changed.
- **GAMP Software Category 4 (yellow): Commercially available, configurable product.**
  The business process within the software can be changed to match the proposed laboratory process. Nonetheless, you can configure it in a range of different ways.
- **GAMP Software Category 5 (red): Custom or bespoke modules and applications.**
  This also includes custom or bespoke modules, which you can put around a Category 4 System.

Category 5 software should only be used if there is nothing on the market with a business case to justify the expense and time of developing, validating and supporting throughout its operational lifetime a unique application. The alternative is to change working practices to use a Category 4 product and configure rather than customize. As FIGURE 6 shows, the risk associated with

the various software categories, and to reduce this as much as possible, it is better to select a Category 4 product and configure.

That said, within Category 4 software there are various options for software configuration listed below with increasing complexity:

- Software switches (e.g., turning an option on or off)
- Parameterization where a function is turned on and a value added (e.g., password expiry date)
- Graphical configuration (e.g., drag-and-drop configuration of reports)
- Calculations (e.g., using a spreadsheet functionality)
- Supplier language to configure the application
- Programming language to add modules of functionality to the core application

All configuration approaches must be controlled and documented but the last two are classified by GAMP 5 as custom software that need to be managed as such (21).

The Road to Digital Transformation

How have these concepts and requirements been translated into Agilent products? Let's start by defining what a digital laboratory really means.

A digital laboratory is not a goal by itself but a means to an end. We want to achieve a laboratory working in the most efficient way and minimize the errors. Examples of the achievements when a laboratory has been digitalized are:

- No paper to document the work following elimination of hybrid systems.
- Analysis without touching a keyboard or a mouse
- Immediate access to acquired data by all peers
- Preventing the use of assets that are not fit for purpose such as the non-calibrated instruments and use of expired solvents or reference standards
- Ability to detect errors immediately
- Obtain assistance from the system to identify all the potential issues with review by exception.

Let's elaborate a little bit more about all of this. A laboratory operation is complex and very heterogeneous. Although the overall analytical process shown in FIGURE 1 is similar in all laboratories, the detailed operations in an individual laboratory are different. The reason is a very high number of variables that are involved. For example, there are different types of samples analyzed by different analytical procedures by instruments that inevitably end up being unavailable or not calibrated. Some analytical instruments are controlled by different software applications that generate data in different data formats. There are also consumables to handle that have expiration dates. Finally, the analytical staff must be competent and trained. All these factors must be controlled to enable compliance with applicable regulations.

Agilent provides several applications for automating any laboratory. Following customer input, we developed an end-to-end analytical

workflow application that automates the analytical process from an analysis request through sample receipt and analysis until its final disposal. Through the application you can manage staff availability, instruments calibration and use, resource planning plus management of chemicals, buffers and reagents. In addition, an analytical procedure can be automated from sample preparation to generation of a reportable result. Following review, the records can be locked to prevent alteration and the final result sent electronically to the analysis requestor. The data can then be retained for the applicable record retention period.

To automate laboratory workflows, we have to go step by step and here are some aspects that we'll have to consider:

- An integrated solution that embeds sample and analysis workflows altogether that manage any kind of techniques and interface different types of analytical instruments.
- All should be connected to a central database to enable efficient collation of data with an overarching audit trail.
- Easy to validate, use operationally, and maintain is essential.
- A flexible and modular solution that enables a laboratory to break down the complexity of methods and SOPs into smaller protocols that you can assign to different people.
- Be able to collate and trend analytical data over time and learn from what you've done in the past.
- All of this under the umbrella of the compliance with the concept of security and integrity covered with our solution. It's fundamental and connecting all the products together makes this much easier.

We've seen that the lab is complex and turning this complexity into a digital solution is not an easy task. However, in the second part, a case study will be presented to demonstrate how to achieve this.

Quo Vadis Laboratory Automation?

If you are going to automate a laboratory, it is not possible to do everything at once. It is essential that you have an automation plan. Coming back to the Stason and the Tender warning letters and the remediation mandated by the FDA presented earlier. These companies will need a plan with demonstrable progress when FDA inspectors return in the future.

To achieve such a plan, it is imperative that there is management input and support they will approve the spend and commit resources to do the work. Management must support the plan both in private and in public. This is critical because the project team is going to work under the manager's delegated authority. But one of the things that you will need with the plan is time to implement the applications. You've got to have support of management for doing that. Really, what you want is a laboratory automation strategy that we will discuss in Part 2 of this series.

Summary

We have looked at the analytical process

from sample management to the reportable result from the perspective of where laboratories are now. The problems are paper records, use of hybrid systems, spreadsheets with manual data input and subsequent transcription error checks that result in inefficient and ineffective processes. This led to a discussion about the cost of compliance versus the cost of non-compliance. It is important to understand that the cost of compliance is always cheaper than the cost of non-compliance. In light of recent FDA warning letters, it is important to automate as much as practicable and some of the applications to achieve this have been discussed. The principles of moving to a digital laboratory and the need for a plan to achieve this were outlined. These latter aspects will be expanded in the second part of this series.

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A Practical Approach to Building an Electronic Laboratory, Part 2

R D McDowall and Nicolas Louvet

Building a holistic laboratory automation strategy.

Introduction

In the first part of this two-part series on a practical approach to building an electronic laboratory, we focused on where we are now. We started with an overview of the analytical process from sample to reportable result. Then, we moved on to understand that the cost of non-compliance (getting caught) is much greater than the cost of compliance (doing it right the first time). The rationale is that a laboratory has to keep up with technology to comply with the *current* in cGMP. We looked at the various laboratory informatics applications that could be used to develop an electronic laboratory and the journey toward a digital laboratory and concluded with the need to plan laboratory automation to be successful.

In this part, we will discuss:

- How to develop a holistic laboratory automation strategy. This will be broken down into several individual projects that will be implemented and integrated together.

- We ask an interesting philosophical question: Does the laboratory fit the product or does the product fit the laboratory? This will revisit the process mapping and redesign discussed in Part 1 because automating an inefficient process is not productive.
- Understand the best way to write user requirements that are testable or verifiable.
- How to involve the users to ensure a successful laboratory digitization project.
- How to prepare for a digital inspection or audit.
- A case study of developing a digital laboratory will be presented.

We will now begin by looking at how to develop a laboratory automation strategy.

Developing a Laboratory Automation Strategy

A laboratory cannot automate all processes at the same time because it must continue analyzing samples otherwise development projects will stop or production batches will not be released. Therefore, a phased approach to laboratory automation is essential and each project should be part of the overall strategy. The strategy will cover the whole laboratory and a single project equivalent to a piece of an overall laboratory jigsaw puzzle.

An input to this process is that processes in the laboratory have already been mapped and are available for the strategy development. If not, then the work described here must expand to include data process mapping.

Laboratory and senior management support. It is critical to have the support of both laboratory and senior management who will fund the strategy and will want to see tangible business benefits as a return on investment. It is not only money; human resources will also be critical. Key staff may be required to work on the automation projects full time and the company must hire additional temporary staff or use a contract laboratory. These costs must be factored into the overall strategy. A word of warning; if staff have to work part time on an automation project, then the project schedule may be delayed if urgent analysis is required. The problem is that urgent analysis never stops and staff are reallocated to analysis. Thus, the full-time allocation of staff is preferred.

Management needs regular and realistic feedback on progress with projects and must be alerted to problems. Positive management backing is essential both in public and in private. One way of this happening is walking through the laboratory and talking with staff about the strategy and listening to any concerns.

Business benefits of the automation strategy. The strategy must make clear that the main business benefits are:

- Standardized, consistent, faster, and simpler working practices enforced by technology solutions that are easier to automate, validate, and train staff to use.
- Elimination of hybrid systems.

"Understanding where the laboratory is now is important as the laboratory strategy moves to identify the possible laboratory informatics application that could be used to automate process steps."

- Electronic working is faster than paper or hybrid work, thus resulting in increased speed of decision making.
- Assurance of data quality and data integrity through the use of technical controls in software.
- Implementing review by exception where informatics applications allow this.
- Automated compliance and transparency of work.
- Use corporate IT standards to enable effective support.

Generate realistic project schedules. It is always tempting to develop aggressive project timelines to impress senior management. This is a recipe for disaster. It is better to undertake detailed planning for each project when it starts and spend time getting the planning right. Include some contingency time that may or may not be used to manage expectations of management and users. Subsequent projects should incorporate key learning points from earlier ones to aid better planning.

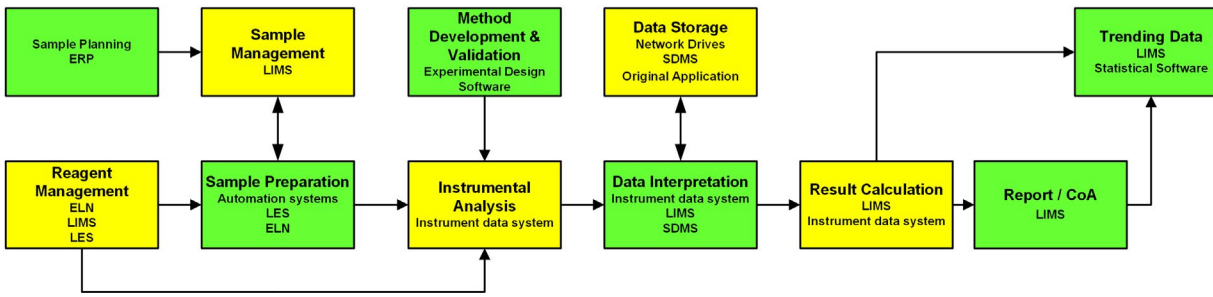
Assess current analytical instruments and systems. The first stage is to assess what instruments and software applications you currently have and evaluate how they are being used now (e.g., hybrid or electronic systems). This is the laboratory baseline. Assess the following:

- What analytical instruments and systems does the laboratory have?
- Are instruments standardized to save on interfacing costs?
- What is the automation potential for the current systems? For example:
  Can instruments be interfaced, if so how?
  Are the applications networked?
  Can they enforce electronic workflows by using the technical controls in each application?
  How does each application ensure data integrity?
  Can an application use electronic signatures?
  The aim is to determine if an application can be used in the future or needs to be replaced in the short to medium term.
- Identify corporate systems to be interfaced to as well as the data transferred to and from the laboratory.

The aim is to identify gaps in automating the laboratory and this leads to the next stage of developing the automation strategy.

Identifying applications to use in the strategy. Understanding where the laboratory is now is important as the laboratory strategy moves to identify the possible laboratory informatics application that could be used to automate process steps. The applications that could be

FIGURE 1: Analytical process steps with possible informatics applications used for automation.



used are shown on each step of the analytical process in FIGURE 1. The question for the automation strategy is how many of these should be considered for the laboratory.

The fewer the number of applications used, the simpler the interfacing requirements. This is where application convergence, discussed in Part 1, can be used to the lab's advantage to reduce the number of applications implemented, validated, and interfaced. An application using the same database for, say, sample management and sample tracking, typically found in a Laboratory Information Management System (LIMS), and electronic test execution, a core functionality of an analytical electronic lab notebook (ELN), can be slowly expanded throughout a laboratory after the first roll-out and is not as disruptive as implementing and validating several different applications.

Map and Improve Processes

As we discussed in Part 1, it is vital that existing processes in the laboratory and the interaction between the laboratory and other parts of the organization are mapped and redesigned. When the current process maps are finalized, three key tasks must be completed:

1. **Identify process bottlenecks.** If there is a significant delay in a specific process activity, it must be documented, and the reason for it understood and eliminated in the redesign of the process. For example, if there is a delay in the second person review, evidenced by piles of batch records on their desk, why is this?
   Is it because there are hybrid systems involved?
   Are data generated in the analysis from multiple locations?
   Do systems lack audit trails?
   Is there a need for cross-referencing manual logbook entries with electronic records?
2. **Identify the analytical instruments to be used or replaced.** From the information gathered earlier, determine if an instrument will continue to be used or replaced. If it is used in standalone mode, can it be interfaced to work electronically? It may seem obvious,

but standalone instruments and those that print out results must be identified and investigated for their feasibility of interfacing to an informatics application such as a Laboratory Execution System (LES) or LIMS.

3. **Identify where and how computer systems are used.** This not only includes the instrument data systems, but also, most importantly, spreadsheets and the calculations that are carried out. You need to think about data inputs to these computer systems, data outputs, and any data transformation. It may be a silly question, but are the computerized systems used in hybrid mode? "Yes" is probably the answer and plans should be made to reduce or eliminate paper output.
4. **Identify the data vulnerabilities.** It is important to identify any data vulnerabilities in the process so that they can be eliminated in each process activity during the redesign. If this work has been completed earlier, the information can be used to save effort.

An Overall Laboratory Automation Strategy: Where Are We Now?

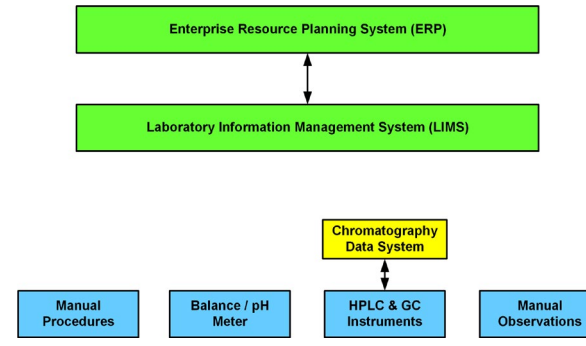
We will now discuss an example of a laboratory automation strategy. The current situation is shown in FIGURE 2 where an existing Enterprise Resource Planning (ERP) is interfaced with an existing LIMS. These systems exchange sample requests and results between them and there is a download of product specifications from the ERP. Nonetheless, the LIMS is not interfaced to any analytical instruments. There is a chromatography data system (CDS) that controls all chromatographs, but it is used as a hybrid system even though it has the capability of working electronically.

The CDS and the LIMS are not interfacing and there is no data capture from manual work such as sample preparation; data from balances and pH meters instruments are printed out and tests by observation are recorded on paper. During the redesign of processes and the development of the automation strategy, the three principles of laboratory automation (introduced and discussed in Part 1) must be applied. This will be discussed later.

Does the Product Fit the Lab or Does the Lab Fit the Product?

Now we come to a very interesting philosophical question: Does the product fit the lab or does the lab fit the product? In Part 1, we discussed the software categories described in GAMP 5 Appendix M4 (1) and we need to consider Category 4 (configured

FIGURE 2: Existing informatics applications in a laboratory.



software) and Category 5 (customized software) in this discussion.

The first option is the product fits the lab.

- The assumption is if the product fits the lab your processes are efficient.
- The problem with that approach is that not many processes are that efficient in many laboratories. As we saw in Part 1, processes have evolved over time, especially if you've had a kicking from an inspector or have been publicly humiliated by senior management.
- If this approach is taken, it might result in extensive configuration or, even worse, customization of the software. This will be time consuming and expensive, and your validation costs will go through the roof.

The second option, where the lab fits the product, is the road best traveled.

- Changing your lab processes to be as close to standard product functionality is a better and faster option provided your business objectives are met.
- There will be configuration to ensure the protection of electronic records and eliminate data integrity vulnerabilities.
- This approach is quicker to implement.
- Supplier testing can be leveraged to reduce validation time and costs.

Fitting the lab to the product will result in process efficiencies with improved working practices and regulatory compliance. An outcome of this will require an updated set of user requirements that will be discussed later in this article.

Applying the Three Principles of Laboratory Automation

This section deliberately reiterates some content from Part 1, but also goes into more detail to understand what is required. Let us see how these are applied when we consider an existing laboratory setup (a) that is transformed into an overall laboratory automation strategy (FIGURE 3).

Principle 1: Data capture at the point of origin. Data should never, ever be written down on paper, a body part, a lab coat, or even a Post-It note. Ensure that data are captured securely by interfaced instruments and that applicable ALCOA+ principles are met. In the strategy shown in FIGURE 3, an LES is used between the LIMS to automate manual processes and interface instruments. The LES is used to:

- Automate manual procedures such as sample preparation and capture observation tests.
- Interface analytical instruments so that data generated by them can be integrated into the newly automated procedures above. This means that instead of writing up the preparation of a buffer solution manually in a logbook, the automated process in the LES will state what compounds will be required and the weights of each are captured electronically. When the solution is

FIGURE 3: Example of an overall laboratory automation strategy.

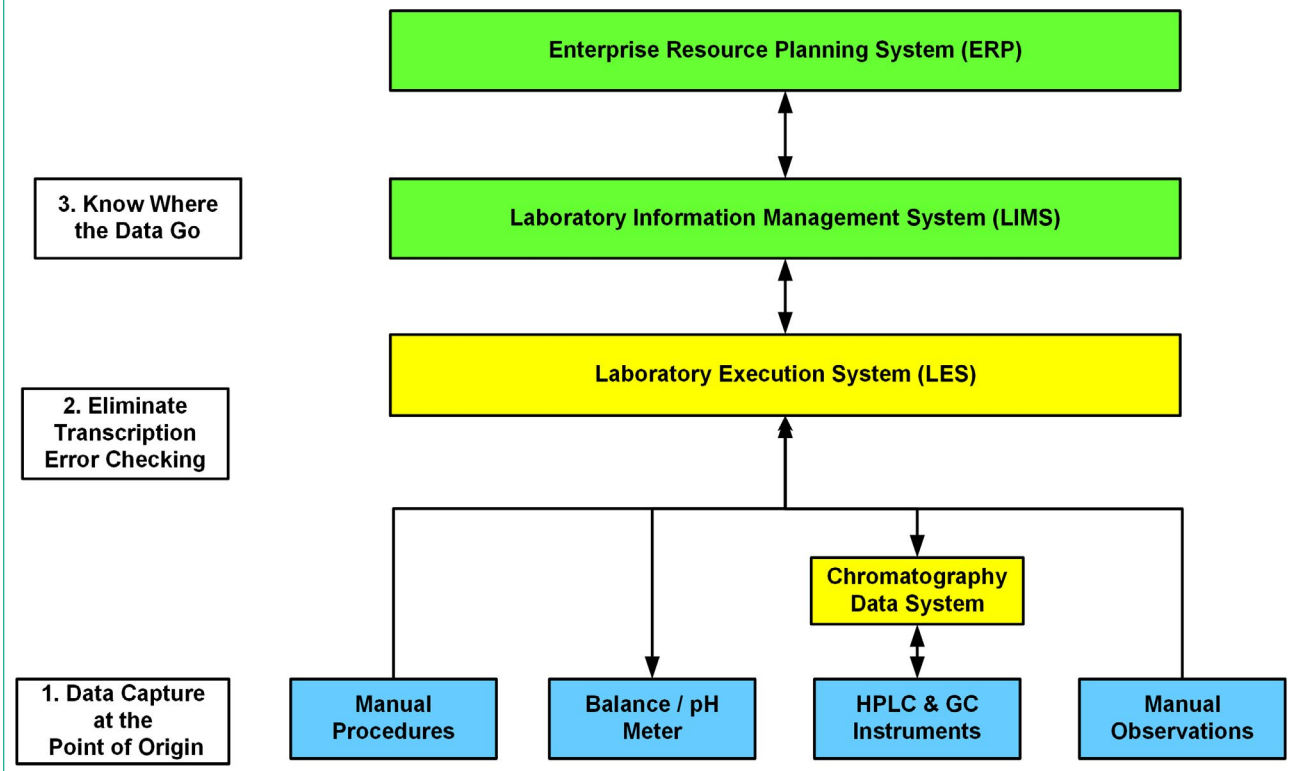
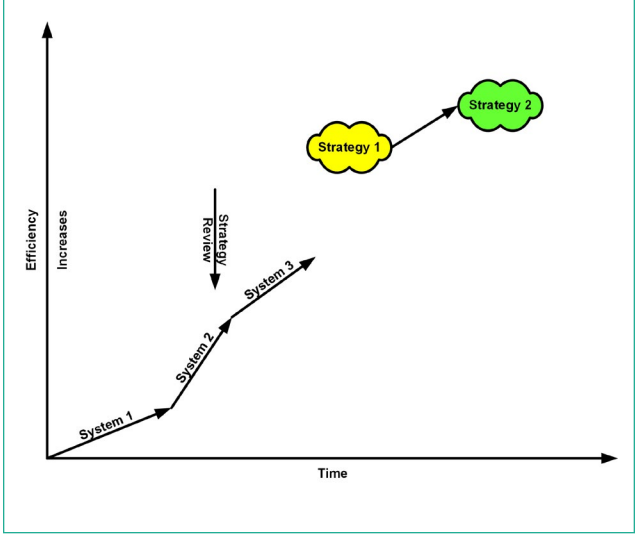


FIGURE 4: Conduct regular review and revision of the laboratory automation strategy.



prepared, a label is printed containing information such as buffer name and strength, preparation and expiry dates, and who prepared it. There would also be a reference to the records in the LES.

- Manual observations would be entered directly into the LES without the need to record the result on paper.

Overall, this approach would eliminate the use of master templates and blank forms from the laboratory and the administrative overhead of managing them (2-4).

Never transcribe data. Once data are captured electronically, they must not be printed to be manually and entered

elsewhere in another computer system. The advantage is that transcription error checking is eliminated as the transfer is by validated electronic processes. However, such data transfer should not be performed by a USB stick or other removable media as this has resulted in FDA citations (5, 6).

- Sample information and analysis requests are downloaded to the LES to carry them out and results are uploaded to the LIMS.
- Sample management can be conducted either in the LES or the LIMS as designed.
- The CDS workflows are changed to eliminate paper and use electronic signatures.
- The CDS and LES are interfaced to eliminate manual data entry and transcription error changes.

Know where the data go. This principle is the most difficult to meet because it requires thought and planning. Such planning includes a naming convention for folders and projects in a networked database application such as a CDS, where most of the storage and retrieval is handled via the application. However, this may become more complex for files generated by file-based applications. Regardless of the naming convention used, it is important to store data securely and in known locations so that data can be retrieved for annual or product quality reviews, audits, inspections, or complaints as well as archived for their record retention period. This will require extensive naming conventions if it is not done automatically by any computer system. For example, will the naming convention in QC be based on:

- Product?
- Product and strength?
- Development phase, for an R&D project (e.g., pilot batch)?
- The market?
- What about analyses that are common across all products?

You need to plan for these things upfront. Much of the data storage will be undertaken by the new LES as well as the existing CDS and LIMS, but there must be care in determining the naming conventions. If required, prototype them in a test environment to see if they work acceptably.

"Much of the data storage will be undertaken by the new LES as well as the existing CDS and LIMS, but there must be care in determining the naming conventions."

An Overall Laboratory Automation Strategy: Where Do We Want to Be?

The overall strategy is shown in FIGURE 3, but the question is how would this be achieved? It is possible to undertake a large project to automate everything, but that would take time and carry significant business risk. Instead, the strategy must be broken down into more manageable projects such as:

- A quick win is a small project with big benefits that lend credibility to the overall automation strategy. For example, the CDS has electronic signature capability. Change the CDS from a hybrid system to electronic working by implementing electronic signatures and validating the configuration update. This would replace printing many chromatograms with only printing the summary report as an interim measure.
- Implement and validate the LES platform.
- Interface the CDS with LES and LES to the LIMS. Sample information can be downloaded to the CDS and results could be transferred automatically once the CDS report was signed by the second person reviewer.
- Then, a stepwise approach to specifying and implementing individual analytical workflows, interfacing analytical instruments, and entering manual results directly in the LES can begin.
- While this lengthens the overall implementation, it is less disruptive in terms of laboratory productivity and efficiency gains over time will be seen.
- When analytical balances are interfaced to the LES, the weights can be transferred to the CDS or used to prepare analytical reference solutions.
- Consider standardizing on the same make and model of instruments to reduce overall interfacing costs.

Some words of warning for an automation strategy. We have talked about processes being automated and these should be end-to-end processes and not point solutions. If a process needs an analytical instrument automated, interface it. The issue can be illustrated with sample management. Some laboratories have suggested automating sample management as the first stage of automation. This is wrong. While enabling readable labels and being able to find them easily, there is little business benefit to this approach because samples are not connected with the analysis.

To ensure the credibility of a laboratory automation strategy, start with quick wins and then go for bigger but achievable projects to build on successes as you go forward.

Review and Revise the Strategy

It is important to realize that an automation strategy is not static; it must be reviewed and, where appropriate, revised periodically. Change occurs: interpretation of regulation changes, the business changes, your business may merge with another organization as well as new applications come on the market with old ones disappearing. Therefore, you should conduct regular reviews and updates of strategy over time as shown in FIGURE 4.

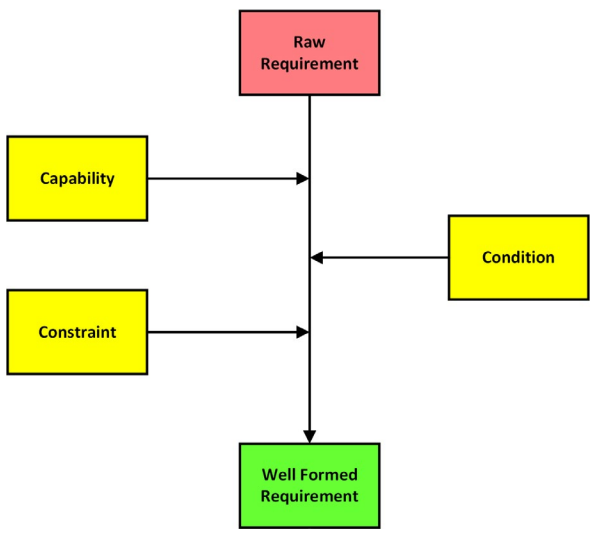
Defining User Requirements

A mandatory part of validation is documenting the intended use in the User Requirements Specification (URS). There will be a generic URS written for system selection. This is critical because without one, you can end up purchasing the wrong application. However, this URS will not be the document to define the intended use

for validating the configured application. It may not contain all requirements you implement or perhaps the application may not undertake certain functions that you have specified in the URS.

Once the implementation team has been trained to use the software, and has developed the final configuration via prototyping, the URS can be updated. Updated process maps can be used as the basis for defining your requirements and even be included in the URS. Each process activity will have inputs, processing activities, and outputs that are useful for defining your requirements. The validation URS must reference the name of the application and version number being implemented either in the title or introduction. This is a living document that will be updated over the life of the system.

FIGURE 5: Transforming raw requirements to a well-formed requirement.



Writing requirements is not an easy task if you are not used to the task. One way to write requirements is described in IEEE Software Engineering Standard 1233 (7). Starting with a raw requirement shown at the top of FIGURE 5, a well-formed requirement has two or three attributes:

- **Capability:** what the function must do (e.g., access to the application is via a password). However, this does not permit any testing, other than a user having a password, as conditions must be added.
- **Condition:** these are what make the requirement testable or verifiable. We need to add to the requirement above a minimum of 10 characters long. We can now test password length at 9, 10, and 11 characters. This could be a well-formed requirement or we could add a constraint.
- **Constraint:** this is imposed on the requirement by either corporate standard or regulation. We could then add to the requirement above that *password complexity must follow IT SOP ABC123 or passwords expire after 90 days.* Alternatively, a constraint can be a requirement in its own right and this helps both risk assessment and traceability. For example, passwords expiring after 90 days can be a separate requirement and with risk assessment you can decide if you want to test a computer clock or not.

"Within any laboratory, there is a formal organization chart, but you also have to take into account the informal laboratory organization or, more appropriately, the Coffee Room Mafia."

Some general advice about writing requirements is:

- Follow the KISS principle (Keep It Simple, Stupid): write short and concise sentences about 10–20 words long.
- Don't write long, complex sentences containing multiple requirements. Traceability and risk assessment become impossible and testing is very difficult.
- It is better to have 10–15 shorter specific requirements than one paragraph of unintelligible and untestable description.
- Never use weasel words. These are words that sound good, but make a requirement untestable.

Let us illustrate the use of weasel words from a case study example where both requirements are uniquely numbered to aid traceability:

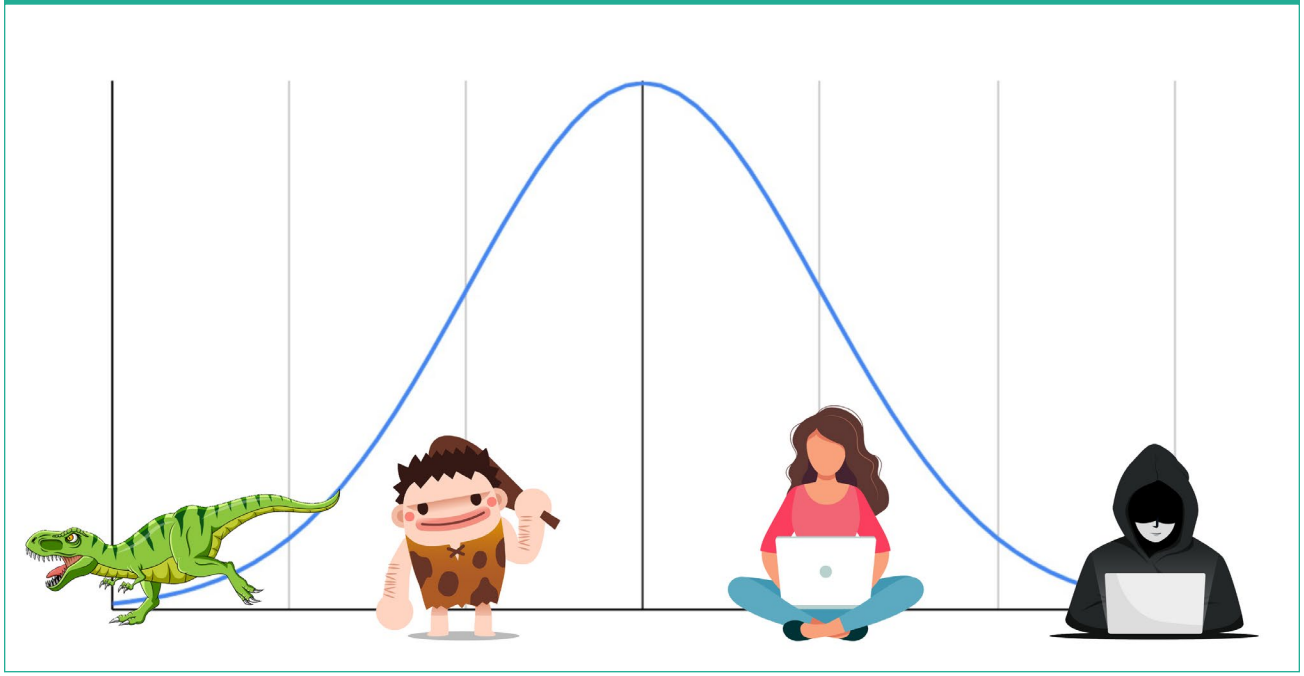
- 6.1.8.1 *"Operating at **normal** PC response with no **undue** delay in response at **low** computer utilization."*
  What is a *normal* PC response time? This depends on the workstation specification.
  What about *undue*? This is a lovely English word and it rolls around the mouth but means absolutely nothing in the requirement above.
  Then there is *low* computer utilization. Are you going to be operating this on the floor or in the basement?
  This is an untestable requirement due to the weasel words.
- 6.2.4.1. *Report production at least one page every 10 seconds at **modest** network utilization.*
  The first part of the requirement is testable and a well-formed requirement. Then come the four words that snatch defeat from the jaws of victory to make it untestable: at modest network utilization. What is a modest network utilization? Are we going to test this requirement when everyone's at lunch or are we going to run this at midnight when there's no one in the building?

You start to see the problems with trying to make your requirements sound good. The best advice is to keep requirements simple.

Involving the Users

Users and their involvement in the strategy and individual projects will make or break your approach. User involvement is critical to the success of any informatics project. You can have the best technical solution in the world, but if you haven't involved the users, the project is highly likely to fail. Users will be involved as subject matter experts to:

FIGURE 6: A continuum of users.



- Map and redesign processes.
- Specify requirements.
- Configure and assess prototypes.
- Write and execute validation test scripts.

Some users may be laboratory administrators for informatics application being the first line of help for other users.

Within any laboratory, there is a formal organization chart, but you also have to take into account the informal laboratory organization or, more appropriately, the Coffee Room Mafia. Some of these users may not be particularly high in the organization, but through force of personality, can break a system and influence other users. To counter this, management must be proactive and reinforce the message that these systems will be used. Perhaps having performance objectives to use the new systems linked to pay would be an encouragement.

In addition, the laboratory must remember that there is a spectrum of users within a laboratory. If we imagine a Gaussian distribution of users, there are four types of users shown in FIGURE 6:

- Hackers are shown on the far right. These users are extremely tech savvy and love working with computer systems, but they also know that there are bugs in the software. They will find them and show you. These users can be very involved in software evaluation and testing.
- Technophiles are the users to the left of the hackers. They like using applications but also understand the limitations

knowing that you're not always going to get it right. They can forgive minor software problems and can offer constructive options for improvement.
- Next are the technophobes, where we start to see some potential problem user groups. Technophobes don't like change, love paper, and don't really like working with computer systems.
- Dinosaurs are on the far left who really don't want to work with computers and you have to spend some time to train this group to work. Therefore, simple automated workflows to direct what the user should do next are essential.

This classification is important as you can use the hackers and technophiles to evaluate new applications, check out prototypes, and then write and execute validation test scripts. Members would also make good laboratory administrators. They will typically be the first users to operate a new system to show that it works successfully. In contrast, the technophobes and dinosaurs will be the last groups to use a new system. However, be careful not to ignore their views and inputs as you may find many are fully paid-up members of the Coffee Room Mafia.

Preparing for a Digital Inspection

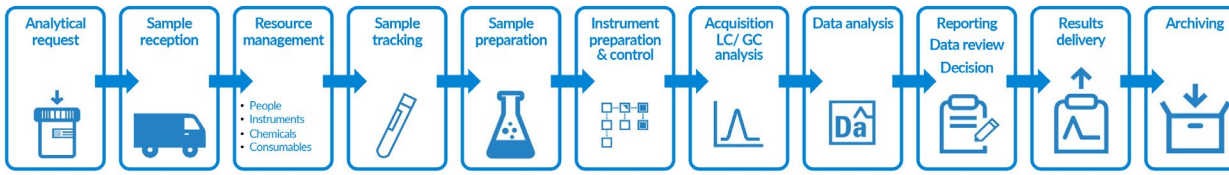
As the laboratory migrates to a paperless operation and becomes electric, the issue of how to handle audits and inspections surfaces. Handling an old-style paper inspection is easy; just bring in the fork lift truck with reams of paper and leave the inspector to it. Times have changed and inspectors want to see the electronic records and audit trail entries on-screen with any computerized system. We need to think about how to handle a digital inspection and how to provide an inspector access to your computerized systems. Inspectors expect computer system access, as question 17 in the FDA's data integrity guidance makes abundantly clear (4).

Do you have an SOP about how you're going to allow inspector access to your systems? As an inspector has not been trained on your system and its specific configuration, are you going to give them access by themselves? Alternatively, are you going to provide an expert user who knows the system and to operate it under the inspector's direction? The latter option is much better than the former as you don't want to encourage an inspector's fishing expedition.

Prepare for questions on:

- Who decides that an individual will be a user?
- How is this authorized and implemented?
- Checks of users who have moved or left the company have had their accounts disabled.
- Set up of user access privileges.
- Which users have deletion privileges (a hint here: nobody).
- How conflicts of interest between users and administrators are avoided.
- Have application-specification documents available as these will be checked against the actual software settings.

FIGURE 7: Case study of an analytical workflow.



Otherwise, you can end up doing a pretty good impersonation of a goldfish gasping for air.

Other areas to consider:

- How will requests be handled for access to review batch analysis records?
- How transparent are actions by users?
- Are you integrating into compliance?
- How are data transfers between other systems carried out?
- How are second person reviews including a review of audit trail entries carried out?
- Are you reporting all data?
- Be prepared for searches for short runs, aborted runs, and any duplicate data.
- If there is a short run due to an instrument malfunction, there should be corresponding entries in the instrument log book, with requalification if required.
- If the root cause of all out-of-specification (OOS) results are due to human error, this will be cause for further inspection of electronic records.

This gives you an idea for how to prepare for an electronic audit or inspection.

Case Study: Automating a Regulated Laboratory

A case study, based on our experience, will be used to present what a practical solution could look like in a regulated laboratory. We will start with looking at the entire analytical workflow shown in FIGURE 7 and the steps that have been automated.

- An analytical request starts the whole process and it is the initial list of samples and tests that will determine the work that will be done in the in rest of the workflow. The request and sample are raised by someone outside of the laboratory and then after the sample has been taken, it is transported to the laboratory.
- When the sample is received in the laboratory, the sample information and shipping information are captured manually.
- Before starting analysis, the lab manager must have an overview of what resources (e.g., staff and instrumentation) are available to complete all the analytical work.
- Sample management is required to track a sample's progress through the laboratory.

- Analysis begins with the suite of tests requested being carried out: sample preparation, instrument preparation, analysis, data acquisition, processing, and calculation of results.
- Second person review and report generation for the analysis requestor.
- To complete the process, the sample analysis records are archived.

To automate all these steps for the customer, Agilent proposed SLIMS, a Laboratory Execution System. SLIMS brings together the best of sample management and electronic test execution features for all the users in a laboratory such as the lab manager, the technician, and the analyst. The software is designed for the people that work at the bench with workflow capabilities covering all activities shown in FIGURE 7. One of the key advantages of the product is fast implementation. Let's see in detail how that works.

Laboratory overview. Our case study example is a large pharmaceutical company that had a quality control laboratory that required automation together with ensuring regulatory compliance. This project illustrates the importance of starting with realistic ambitions and an iterative approach to implementing electronic workflows. Initially, the customer lacked an overview of the activities in the laboratory, and they wanted a comprehensive solution to manage their samples, data, and procedures. They also required that their existing analytical instruments and systems, especially the CDS and analytical balances were integrated and interfaced into the solution. The aim was to have all data in a single location.

Project approach. The project was established in close association with the customer's quality and regulatory team to ensure that the solution we were building met their needs. The goal was to bring all the data in one place and replace many applications that could not communicate with each other. Working with key users who acted as subject matter experts an interactive approach was taken to the design and implementation of workflows within SLIMS. The aim was to:

- Standardize where possible
- Develop modular protocols
- Implement a quick win, as discussed earlier in this article, to show the benefits of the system
- Iterate with other processes

Progress was achieved in regular workshops where the goals and prototypes of a workflow were reviewed by key analysts/SMEs who had a vested interest as they would be using the software operationally. This was an opportunity for the laboratory to reassess their ways of working; keeping some of their processes and redesigning others before implementing them in the application.

The first workflow. The project started with a simple, generic workflow that covered several methods in the laboratory so the different stakeholders would learn about

" A product submitted for testing must trigger all analytical procedures appropriate for the product monograph within SLIMS."

digitization of the laboratory processes. The first phase focused on improving the collaboration between the quality laboratory and the manufacturing team.

- The current process is paper based: there is a manual and paper analysis request form on which they define the information about the sample and the tests required.
- The redesigned workflow in the system defined the sampling and shipping instructions so that at the time of the request creation, the manufacturing team has access to this guidance (e.g., data capture at the point of origin).
- After this, all work will be performed using SLIMS (e.g., never retype data). This enables manufacturing to find out the status of the analysis on-line with an estimate of when the final report will be available, highlighting the sample tracking capabilities.
- The location of the sample can be defined and enabled in SLIMS based on sample properties such as type or user-defined metadata such as sample status. As samples are composited, mixed, or aliquoted, they can be tracked by the system individually along with their relationship to the original sample.
- SLIMS also provides full barcode support with a label designer function. Each sample has its own identifier, but also the barcode that can be placed in the sample container or vial.

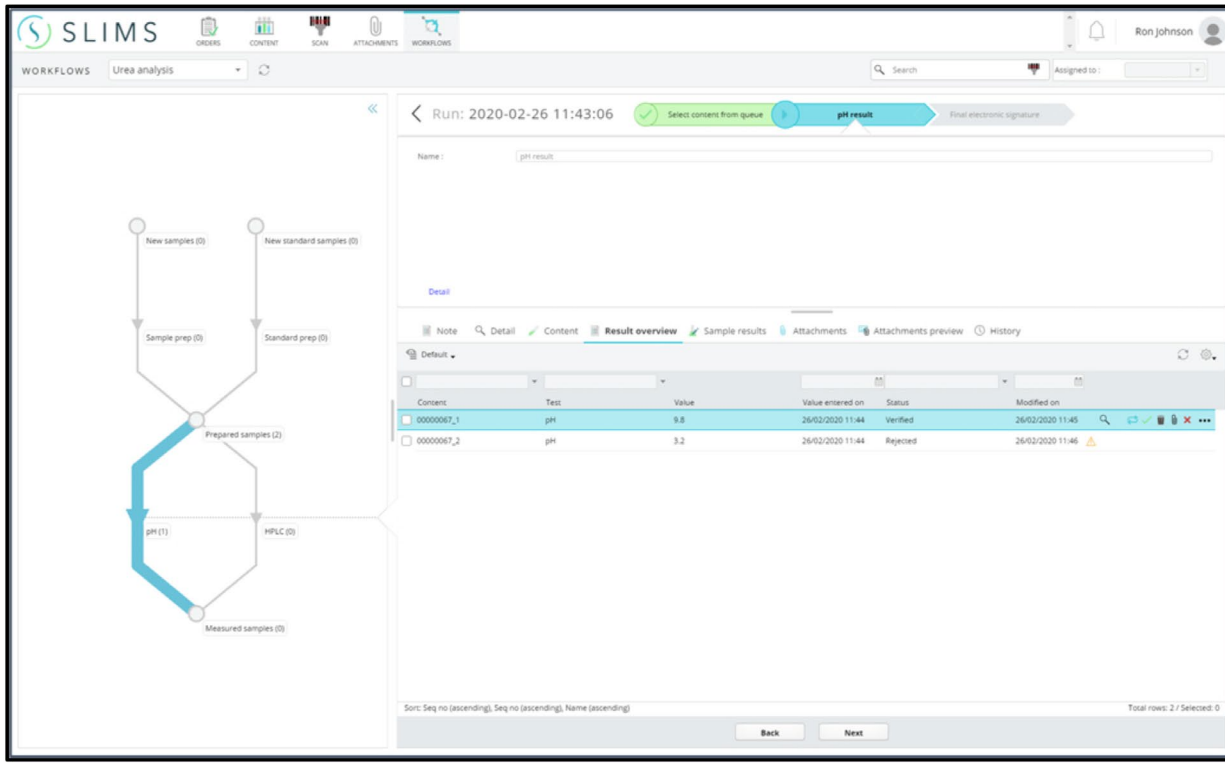
To aid faster implementation, there is a SLIMS Store website where customers can download some operational workflow snippets and build entire workflows out of them. In this example, the customer could download different sample metadata snippets and therefore expedite workflow construction.

Checking laboratory resources. SLIMS provides the means to check the resources of the laboratory before use, for instance, if an instrument is out of qualification or calibration cannot be allocated for use in an analysis.

Implementing analytical procedures. A pharmacopoeial product monograph contains the legal requirements for testing along with minimum specifications that each batch must comply with to be marketed. Each monograph can contain several tests that must be carried out and this is where we meet the complexity of a regulated GMP laboratory. A product submitted for testing must trigger all analytical procedures appropriate for the product monograph within SLIMS.

- Each paper analytical procedure must and can be implemented in the LES. The process starts with a very simple generic workflow to visualize the

FIGURE 8: Results in an electronic workflow.



workflow, which is broken down into more detail to define the data to be acquired and processed. Feedback from the stakeholders is an essential input to ensure that the electronic workflow is correct.

- The process is matched with SLIMS modules or protocols to start automating the procedure within the application. A protocol can span multiple steps or be as simple as requesting the retrieval of a single result. It is easier if complex workflows are broken down into simpler modules or protocols to help understand and automate the process.
- Where necessary, a module can incorporate interactive note taking for step-by-step recording of experimental data by an analyst (e.g., contemporaneous).
- A procedure can also include calculations as a result of weights, dilutions, puritie, and so forth.
- Any workflow can incorporate modules for connections to analytical instruments such as balances and pH meters to ensure that data are captured at source and avoid paper printouts.
- Integration with the chromatography data system was achieved so transfer data and results electronically between the LES and CDS.
- Second level approval follows before

the final release of the result report. It is also possible to highlight if a result is out of specification or warnings can be displayed to the users.
- After issue of the report, the data are archived for the records retention period within a single repository and linked together (e.g., know where the data go). This drastically simplifies all the data searches later on.

This results in an electronic workflow shown in FIGURE 8; the arrows represent a protocol and the sequence of actions that the user must follow. As each analytical workflow is executed, specific instructions are given to an analyst to be executed. The circles represent the samples that are in the queue and are waiting to be used in one of the protocols.

To train users, an SOP was developed and linked to specific projects and experiments within the application.

Case study summary. The interface between production and the laboratory is automated: production submits sample requests and receives a certificate of analysis (COA) summarizing all results. When the COA is approved, the report is shared automatically with the requestor. The customer has been using the product for some time and has plans to expand by adding more techniques into SLIMS.

For the customer, the software and it is now a source of satisfaction because they take advantage of the benefits of the product. By first simplifying the infrastructure, their audit was much easier than it had previously been. Also, they can now see the different bottlenecks within the laboratory, which allows process improvement including measuring turnaround time for samples.

Summary

A laboratory automation strategy with planning before implementation is preferable to simply throwing money at a laboratory problem. It is important to realize that informatics solutions do not have on buttons. It requires much planning, thought, effort, and commitment to automate not only the laboratory but also the interfaces with analysis requestors and the users of the analytical information generated by a regulated laboratory. This is the rationale for a laboratory automation strategy, looking at the order in which systems will be implemented and why we need management support. It is also essential to map and redesign your processes, and eliminate bottlenecks and data vulnerabilities. Above all, don't forget the user community; how they can help and contribute to projects; after all, they will use a system and if they don't like it, they will find informal ways around it.

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