A Practical Approach to Building an Electronic Laboratory, Part 1: Where Are We Now?

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To discuss a practical approach to an electronic laboratory, we need to understand the problems that prevent electronic working. This article will review the following:

- The analytical process.
- Balancing the costs of compliance and non-compliance.
- Mapping and redesigning your processes.
- Laboratory informatics applications.
- The journey to digital.
- Strategic approach to laboratory automation.

THE ANALYTICAL PROCESS

The analytical process in FIGURE 1 describes the high-level workflow from sampling to a reportable result; here, we will focus on sample preparation to reporting in order to make a decision (e.g., for product development or batch release).

More data and information are generated through the process in FIGURE 1 until the reportable result is generated. The underlying data must have:

- Data integrity attributes (e.g., meet ALCOA+ criteria) to trust the numbers generated.
- Data quality criteria (e.g., format, accuracy, timeliness) to make the correct decision.

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

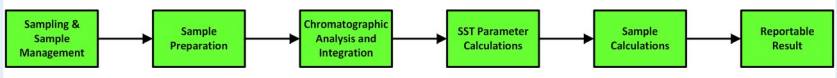
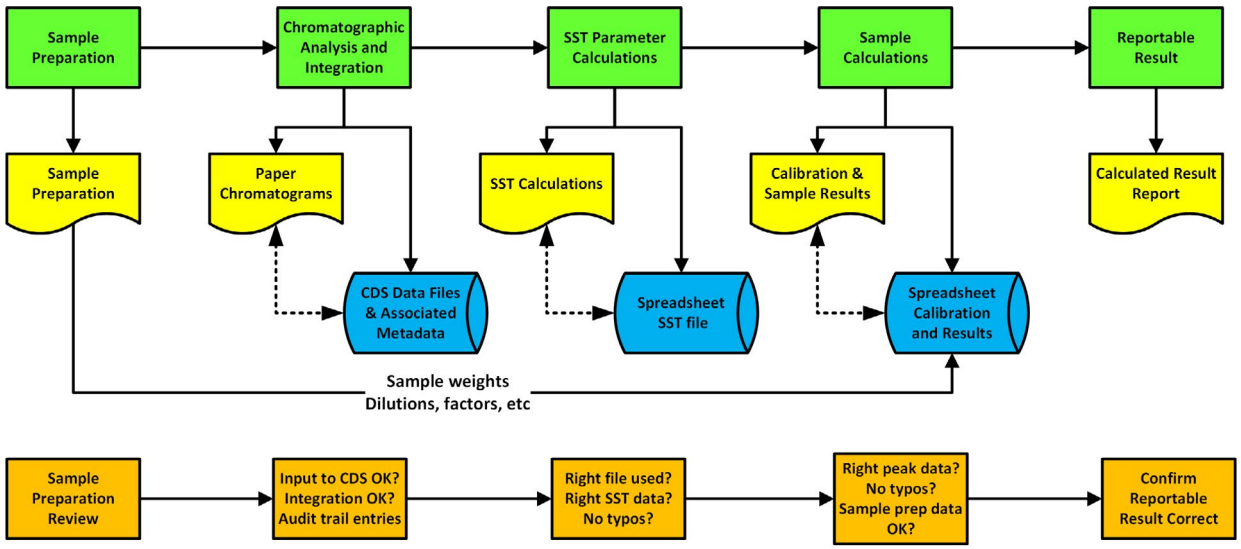


Figure 2: An analytical process involving hybrid records.



LABORATORY PROCESSES EVOLVE OVER TIME

Most laboratory current processes have evolved over time and are not designed to meet today's needs. An example of a chromatographic process in FIGURE 2 illustrates the problem:

- Green is the analytical process.
- Yellow and blue are the paper and electronic records respectively produced.
- The chromatography data system (CDS) measures peak areas. One spreadsheet calculates system suitability test (SST) parameters and a second is used to calculate the reportable result.
- Orange is the reviewer that confirms the analysis is correct, complete, and accurate.

Examining FIGURE 2, we see:

- Sample preparation is manual, generating paper records.
- Data must be typed into the CDS and the spreadsheets, which is a slow and error-prone process.
- Three computerized systems are involved in the process.
- A spreadsheet is used to calculate SST parameters, but the CDS does this automatically thereby negating the spreadsheet.

Again, this process is inefficient, slow and error prone due to the manual data entries, which causes major problems for the reviewer. The reviewer must check the CDS not only to ensure correct integration and audit trail entries for any data changes, but also all manual entries to the CDS and the spreadsheets. This is a painstaking, slow, and tedious task requiring concentration to cross-check between paper records and electronic data. Poor process design results in a review taking longer than the analysis.

THE HYBRID NIGHTMARE

The WHO guidance document states that hybrid systems are not recommended and

should be replaced. The reason is that there are two incompatible record formats to manage and synchronize throughout the retention period. If e-records are updated, a second set of paper is printed, but how can you reconcile the electronic records with the first and second sets of printouts? Eliminate hybrid systems and work electronically.

SPREADSHEETS SLOW DOWN A PROCESS

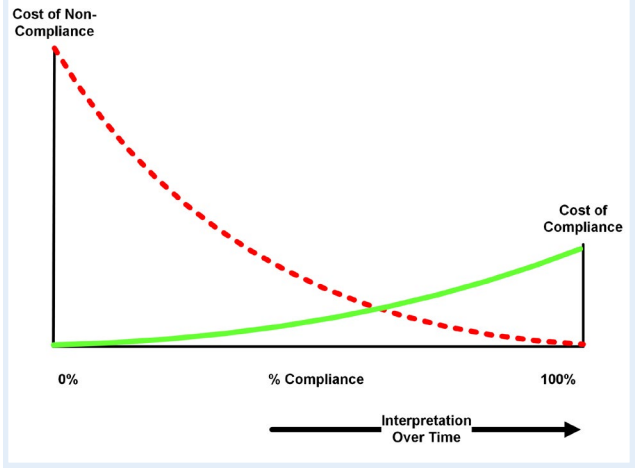
A spreadsheet is a computerized system and a hybrid system. Why are spreadsheets used when there is manual data entry and subsequent transcription error checking? The problem is that spreadsheets are installed on most workstations. Instead of using the CDS to calculate SSTs and results, analysts take the easy spreadsheet option with little thought of the consequences.

UNDERSTANDING THE COSTS OF COMPLIANCE AND NON-COMPLIANCE

Managing risk is a key GMP requirement that requires a scientifically justified and documented risk assessment that balances the costs of compliance and non-compliance. This determines how much regulatory and business risk a company wishes to mitigate or carry.

The left and right axes in FIGURE 3 are the costs of non-compliance and compliance, respectively. The former is much bigger than the latter because fixing a regulatory problem in a warning letter is always more expensive than doing the right job first time. The horizontal axis is the percentage of compliance from 0% to 100%, where nothing is done at 0% and everything possible is done at 100%. The scale is not fixed, but rather moves to the right over time. FDA GMP regulations have changed little since 1978 but the interpretation of them has. Since the Able Laboratories 483 observations stated that audit trail entries were not reviewed, this is now a regulatory expectation. What you are seeing is a shift in percentage compliance to the right as shown in FIGURE 3. Same regulations, more stringent interpretation.

Figure 3: Understanding the costs of compliance and non-compliance.



UNDERSTANDING CURRENT REQUIREMENTS IN CGMPs

Both FDA and EU GMPs have the requirement either in guidance or in law for industry to keep up with technological advances that are both feasible and valuable in assuring drug quality. What this means is what you did a few years ago is becoming out of date as the compliance interpretation moves to the right in FIGURE 3.

Read the Tender Corporation and the Stason Pharmaceutical FDA warning letters or their interpretation to understand the impact of current. The key remediation required by the FDA was:

Instead of buying different applications, try to purchase one to automate multiple tasks and interface with instruments to meet the three automation principles.

Technological improvements to increase the integration of data generated through electronic systems from standalone equipment ... into the LIMS network.

A laboratory should be improving processes rather than waiting for citations to start the work. Never assume that what was good enough at the last inspection will be good enough for the next one. Lack of data integrity with hybrid systems will sooner rather than later come with greater cost if forced on a laboratory by a regulator.

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).
- Electronic laboratory notebooks (ELN).
- Laboratory execution system (LES).
- Instrument data system (IDS) (e.g. CDS).
- Analytical instruments for analyzing samples with the ability to interface with the informatics applications above.

There are three basic principles for automating a laboratory:

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 typed into another application
3. **Know Where the Data Will Go**
   To ensure data can be retrieved quickly, define file and storage location naming conventions

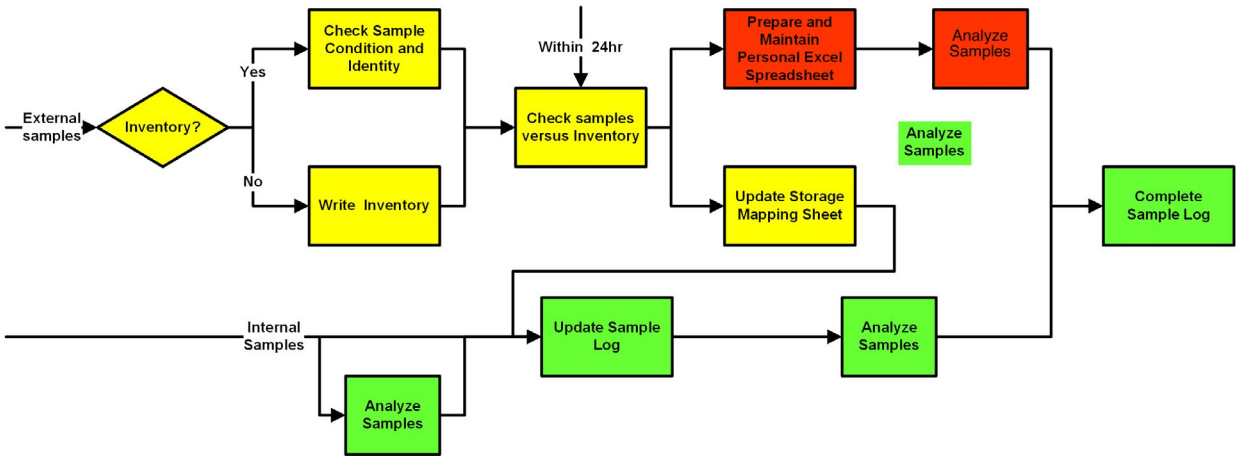
To implement these principles, start from the instruments and the analytical processes. Consider what types of data are acquired, for instance:

- Text or observations (e.g., odor and color).
- Single values (e.g., pH meters and analytical balances).
- Complex data (e.g., chromatography or spectroscopy).

These areas must be assessed and interfaced to networked, not standalone data systems. To ensure and enforce data integrity and regulatory compliance technical controls are enabled, which informatics application are we going to use: LES, LIMS, or ELN?

Be aware of application convergence, where one application type offers the functionality of another (e.g., LIMS with LES functions or LES with sample management). Instead of buying different applications, try to

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



purchase one to automate multiple tasks and interface with instruments to meet the three automation principles.

MAP AND UNDERSTAND YOUR CURRENT PROCESS

FIGURE 2 gave an overview of a poor process, but more detail is required to understand your processes. Laboratory processes must be simpler, efficient, and effective—before implementing any informatics application. FIGURE 4 shows sample management:

- External (yellow) and internal samples (green) are treated differently.
- External samples are checked versus inventory within 24 hours due to samples being lost previously.
- There are branches dependent on the availability of an inventory.
- An undocumented process (red) is used by one person instead of SOPs.

This is too difficult to automate and must be redesigned by simplifying it as shown in FIGURE 5 with the advantages of a single process, which is easier to validate and train staff.

AUTOMATING THE PROCESS: IMPACT OF GAMP SOFTWARE CATEGORIES

Mapping and redesign have only been conducted on paper. How is this implemented in software? Consider the impact of software applications that could be used. The GAMP 5 software categories are the best way to understand this as shown in FIGURE 6:

- **Software Category 3 (green):** Commercial non-configurable product. You cannot change the business process being automated by the software.
- **Software Category 4 (yellow):** Commercial configurable product. The application can be changed to match a laboratory process
- **GAMP Software Category 5 (red):** Custom or bespoke software modules and applications.

Figure 5: The redesigned and simplified sample management process.

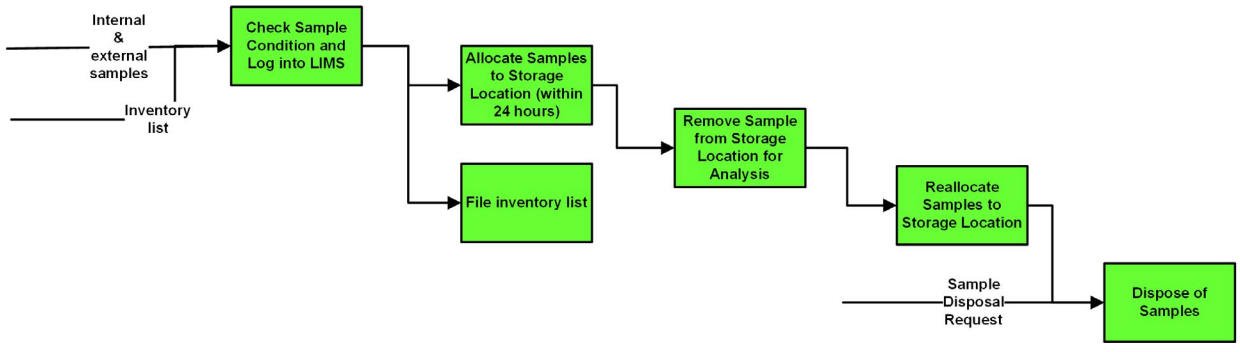
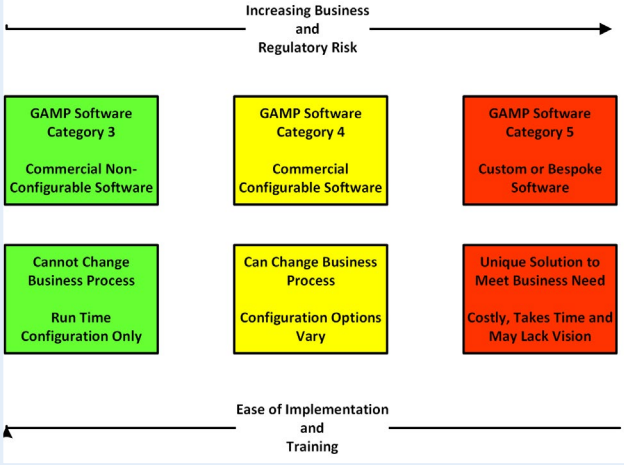


Figure 6: Spectrum of software applications, according to GAMP 5.



This also includes custom modules integrated with a Category 4 System. Avoid this software unless there is nothing on the market and can justify the risk and expense. Alternatively, change working practices and use Category 4 software.

Category 4 software has options for software configuration below with increasing complexity and risk:

- Software switches (e.g., turning a function on or off).
- Parameterization where a function is turned on and a value added.
- Graphical configuration (e.g., drag and drop configuration of reports).
- Calculations (e.g., using 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.

THE ROAD TO DIGITAL TRANSFORMATION

How have these concepts and requirements been translated into Agilent products? A digital laboratory is not a goal but a means to an end (e.g., efficient working, paper elimination, and error reduction). The process in FIGURE 1 is similar in all laboratories, and details can vary tremendously in an individual laboratory due to sample types, working practices, and analytical instruments. Instruments are controlled by different software applications

that generate data in different data formats but must be interfaced as well as managing consumables, plus analytical staff must be trained and competent. All these factors must be controlled to enable compliance with applicable regulations.

Agilent has developed an application that automates analytical workflows from request through sample receipt and analysis until its final disposal. The application can manage staff availability, instrument calibration and use, resource planning plus management of chemicals, buffers, and reagents. An analytical procedure can be automated from sample preparation to the generation of a reportable result together with the review. Then the records can be locked to prevent alteration and the final result sent electronically to the analysis requester. Records can then be retained for the applicable record retention period.

In order to automate laboratory workflows, we have to go step by step. Here are some aspects to consider:

- An integrated solution that automates analytical workflows with instrument interfacing.
- A central database with an encompassing audit trail.
- A flexible and modular solution that manages complexity by breaking complex processes into smaller protocols assigned to different people.
- Collating and trending analytical data over time and learning from what you've done in the past.
- Easy to validate, use operationally, and maintain are essential.
- Technical controls for ensuring data integrity and regulatory compliance.

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 that requires senior management input and support. This is critical as the project team will work under management's delegated authority. But one of the things that you will need with the plan is time to implement the applications. What you want is a laboratory automation strategy, which we will discuss in part two.

SUMMARY

The problems with many laboratories are paper records, use of hybrid systems, spreadsheets with manual data input, and subsequent transcription error checks that result in inefficient and ineffective processes. 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 with management support are essential.

A Practical Approach to Building an Electronic Laboratory, Part 2: Where Do We Want to Be?

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In the second half of a two-part series on practical approaches to building an electronic laboratory, this paper will cover:

- Developing a laboratory automation strategy.
- Does the laboratory fit the product or vice-versa?
- Writing user requirements.
- Involving the users.
- Preparing for a digital inspection.
- Case study of the implementation of a digital laboratory.

DEVELOPING A LABORATORY AUTOMATION STRATEGY

A phased approach to automation is essential to keep a laboratory operating at the same time as automating processes. Inputs to strategy development are:

- Process maps with bottlenecks and ways to eliminate them by automation.
- Management support for strategy funding.
- Identifying business benefits (e.g., electronic working, elimination of hybrid systems, faster decision making).
- Assessment of current instruments and systems: Can they be used, upgraded, or replaced?
- Corporate systems with which to interface.
- Gaps in current automation of the laboratory are seen and this leads into developing the automation strategy and identifying the individual projects within it.

The next stage is to identify applications to implement and plan automation projects:

- FIGURE 1 shows applications that could be used, but application convergence can reduce the number of

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

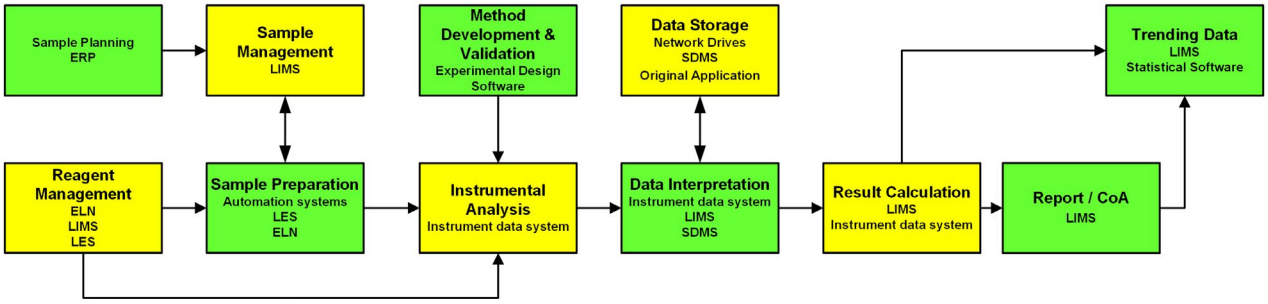
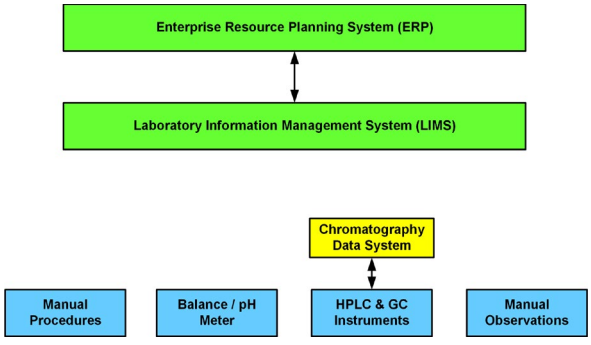


Figure 2: Existing informatics applications in a laboratory.



solutions to implement. For instance, if one application offers both laboratory information system (LIMS) and electronic laboratory notebook (ELN) functionality, this should make implementation easier and can be phased over time so as not to be disruptive.

- Plan realistic schedules with contingency for on-time delivery of projects

MAP AND IMPROVE PROCESSES

Understanding each laboratory process is vital for the successful implementation of any informatics application. Before the automation of a process, laboratories must do the following:

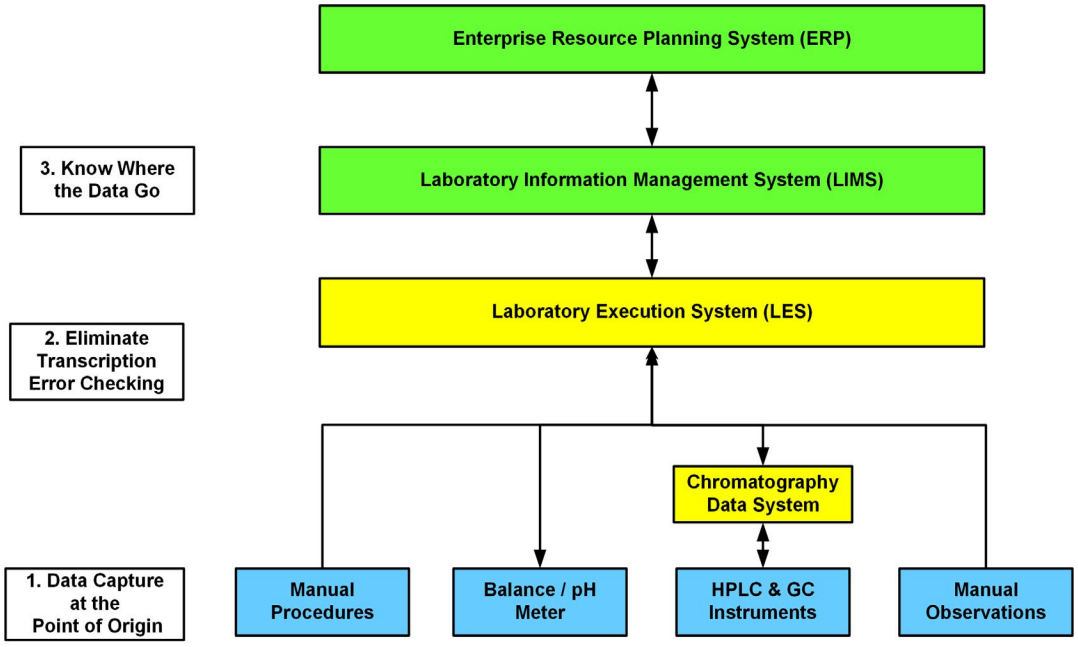
1. Identify and understand the reasons for process bottlenecks and delays, and then eliminate them.
2. Identify the analytical instruments/ systems to be used, updated, or replaced.
3. Eliminate spreadsheets and incorporate the calculations in an informatics application.
4. Identify and eliminate data vulnerabilities to ensure data integrity.

AN OVERALL LABORATORY AUTOMATION STRATEGY: WHERE ARE WE NOW?

FIGURE 2 illustrates the current situation:

- An enterprise resource planning (ERP) system is interfaced to a LIMS for exchange of sample requests, results and specifications.
- The LIMS is not interfaced to any instruments or systems.
- A hybrid chromatography data system (CDS) controls all chromatographs but has electronic signature capability.
- All other work is recorded on paper and collated with instrument printouts.
- Application of the three principles of laboratory automation in strategy development is in two sections ahead.

Figure 3: An example of an overall laboratory automation strategy.



DOES THE PRODUCT FIT THE LAB OR DOES THE LAB FIT THE PRODUCT?

Does the product fit the lab or does the lab fit the product? This is a discussion about configuring or customizing software.
The product fits the lab is not ideal:

- Your processes are efficient (usually not the case).
- Extensive configuration or, even worse, customization of the software is required.
- Increased implementation time and higher validation costs.

The lab fits the product offers a better approach:

- Use standard product functionality, provided your business objectives are met.
- Easier application configuration to eliminate data integrity vulnerabilities.
- Faster implementation and lower validation 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, see later.

APPLYING THE THREE PRINCIPLES OF LABORATORY AUTOMATION

From the informatics landscape in FIGURE 2, we can build a strategy in FIGURE 3 by using the three automation principles.

Principle 1: Data capture at the point of origin. Data are captured electronically and never written down. FIGURE 3 shows a laboratory execution system (LES) to automate manual processes such as sample preparation,

buffer and reference standard preparation, and capture of observation tests as well as interfacing instruments.

Principle 2: Never transcribe data: Once captured electronically, the data must never be printed. The advantage is that transcription error checking is eliminated as data transfer is by validated electronic processes.

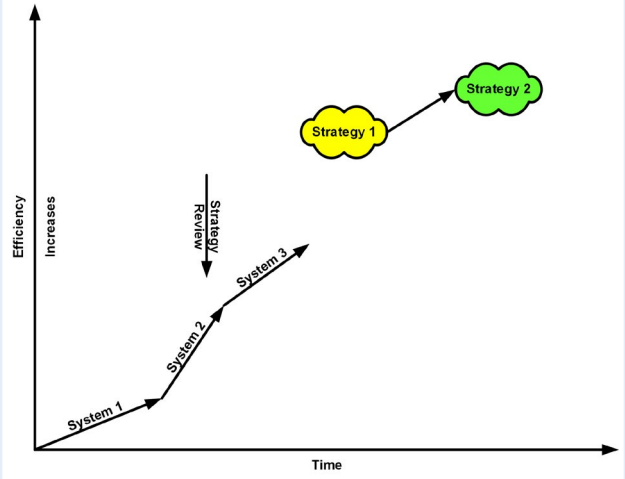
Principle 3: Know where the data go: This requires thought and planning such as creating a naming convention for folders, projects/products, and secure storage locations (if not managed by a database). This will enable rapid retrieval for inspections and so forth.

AN OVERALL LABORATORY AUTOMATION STRATEGY: WHERE DO WE WANT TO BE?

From the strategy in FIGURE 3, the question is how would this be achieved? The strategy needs to be broken down into more manageable projects. Some options are:

- A quick win is a small project with big benefits to lend credibility to the strategy (e.g., the CDS has electronic signature capability. Implement electronic signatures to eliminate printing chromatograms.
- 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.
- Individual analytical workflows can be implemented individually interfacing analytical instruments as required.

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



While this lengthens the overall implementation, it is less disruptive to productivity.

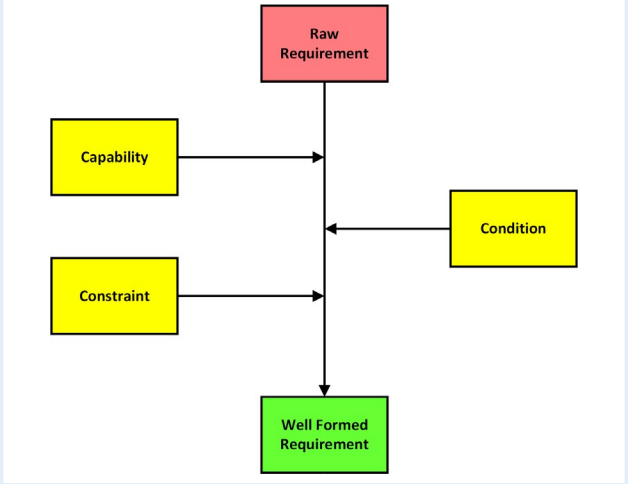
- Interfacing analytical balances to the LES allows sample weights to be transferred to the CDS and so forth.

Processes should be automated end-to-end and not be point solutions such as automating sample management as a first phase of the strategy. This is wrong; while it enables readable labels and enables them to be found easily, there is little business benefit obtained as samples are not connected with the analysis.

Review and revise the strategy. As change occurs, such as when the interpretation of regulations or new applications become available, the automation strategy must be reviewed periodically and updated over time as shown in FIGURE 4.

Defining user requirements. Validation without a User Requirements Specification (URS) is impossible. A URS for selection must

Figure 5: Transforming raw requirements into a well-formed requirement.



be updated as it will not reflect the purchased application. After training to use the system and the final configuration is established, the URS can be updated to include the name and version number of the software used. The URS is a living document that must be updated over the life of the system.

FIGURE 5 shows how to write such requirements, and each must have 2–3 attributes to make it testable or verifiable:

- **Capability:** This is what the function has to do (e.g., access to the application is via a password). However, this does not permit any realistic testing.
- **Condition:** This makes a requirement testable by adding a minimum length of 10 characters.
  Meaningful testing can be conducted. This could be a well-formed requirement itself or we could add a constraint.
- **Constraint:** This is imposed on the requirement by either corporate standard or regulation (e.g., password complexity must follow IT standard operating procedure [SOP] ABC123 or passwords expire after 90 days).

Alternatively, a constraint can be a requirement (e.g., passwords expire after 90 days). Risk assessment and traceability are helped as you can decide to test a computer clock or not.

Some general advice about writing requirements is:

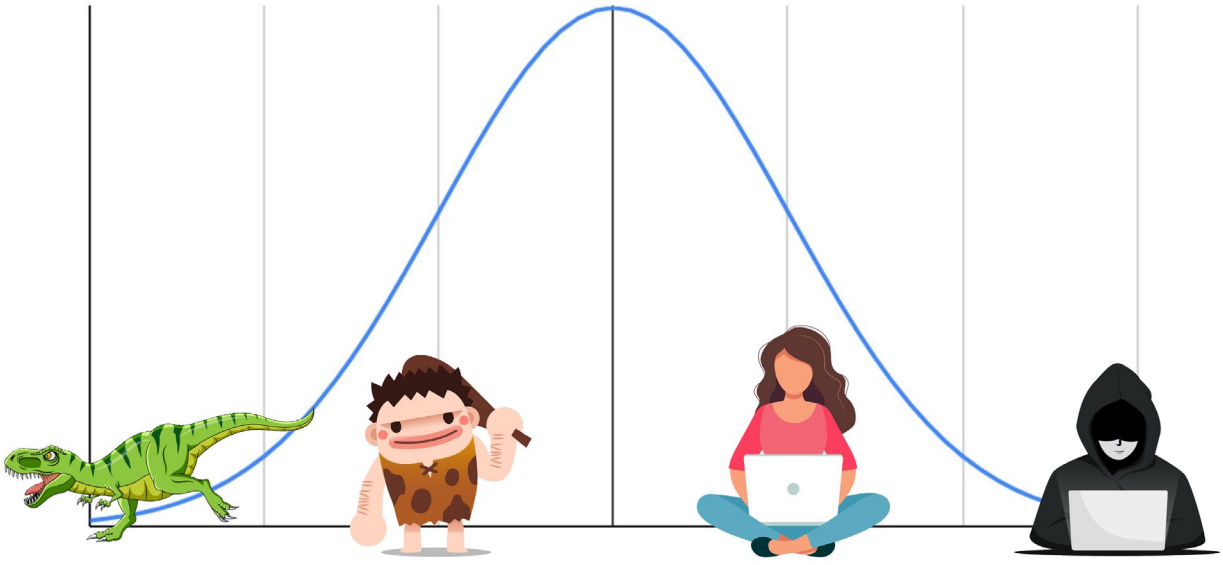
- Write concise sentences about 10–20 words long to help risk assessment and traceability.
- Write 10–15 shorter requirements than one paragraph of untestable description.
- Never use words that are subjective (e.g., user friendly) because they make a requirement untestable.

Involving the users. User involvement is critical to the success of any informatics project and helps in redesigning processes, specifying requirements, assessing prototypes, writing and executing validation test scripts as well as administrating the application in the laboratory. Management must be proactive in encouraging user involvement in projects including performance objectives to use the new systems.

FIGURE 5 shows a spectrum of four user types, from the right:

- Hackers are tech savvy. Knowing there are bugs in software, they point them out; they are useful in testing
- Technophiles like using applications but

Figure 6: A continuum of users.



understand their limitations and can suggest improvements
- Technophobes don't like change, love paper, and don't like working with computers
- Dinosaurs don't want to work with computers and require more training

Simple workflows that enforce user actions are essential.

Preparing for a digital inspection. As inspectors want to see data on-screen; you need to plan how to handle access to your computerized systems. An SOP for this is essential that specifies the laboratory will provide an expert user who will operate under an inspector's direction.

Expert users should prepare for questions on user account management and application configuration. Batch records will be examined including audit trail entries. For a CDS, expect questions on peak integration, searches for short and aborted runs, and checks of out-of-spec investigations.

Figure 7: Case study of an analytical workflow.

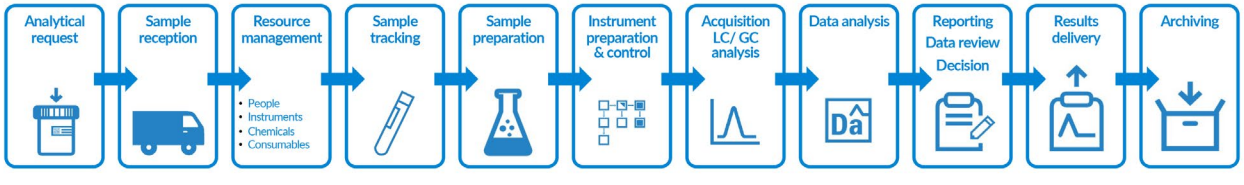
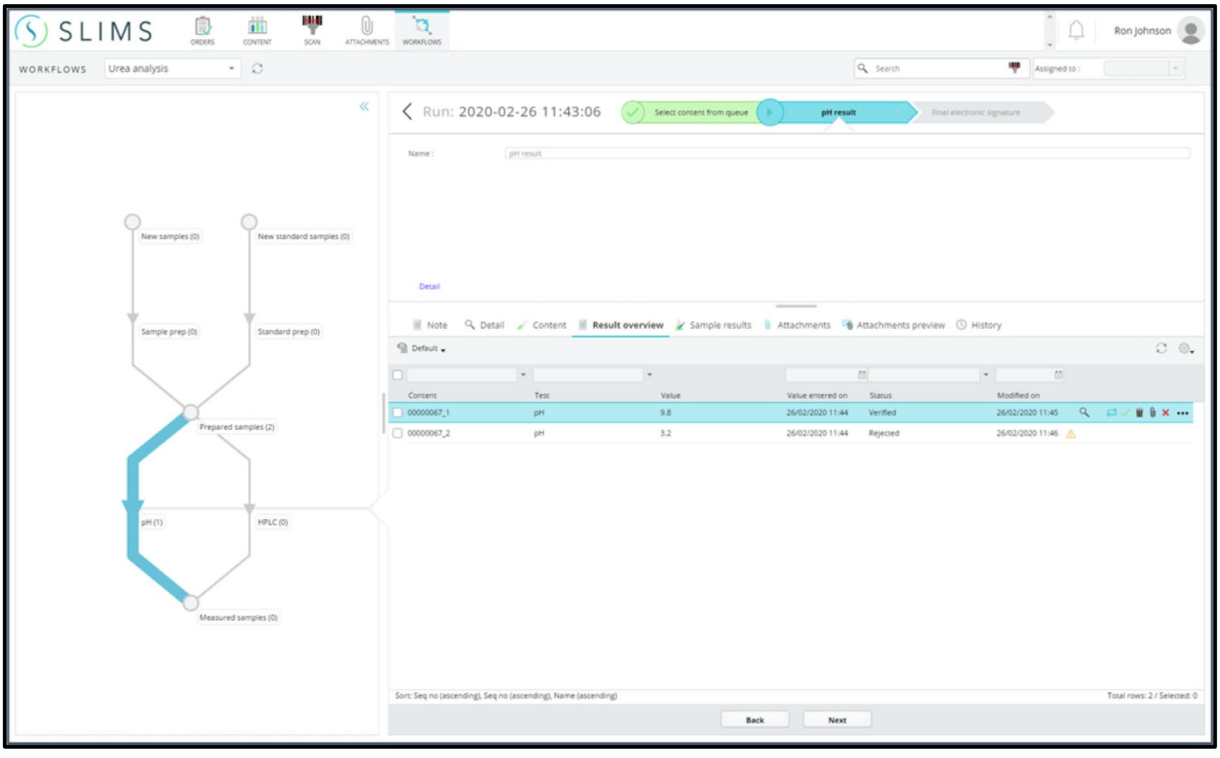


Figure 8: An electronic analytical procedure that has transitioned from paper.



CASE STUDY: AUTOMATING A REGULATED LABORATORY

FIGURE 7 presents a case study where an entire analytical workflow was automated from analytical request to reporting the results and archiving. Agilent proposed SLIMS (an LES) to automate all the activities in FIGURE 7 with the advantage of fast implementation.

Laboratory overview: A QC laboratory of a pharmaceutical company required automation and compliance with a management overview of work. To achieve this, an iterative approach is required to implementing electronic workflows that incorporates existing instruments and systems, especially the CDS and analytical balances. In addition, all data are in a single location.

Project approach: A project team involving QC and regulatory members ensured that the solution met their needs. An iterative approach with user workshops input allowed SLIMS workflows to be developed by assessing current ways of working with some being kept and others redesigned. Where necessary, applications that could not communicate with each other were replaced by SLIMS.

Workflow 1: A simple, generic workflow covering many methods was selected so that stakeholders would learn about digitization, this focused on collaboration between the QC and manufacturing teams. The existing paper process was replaced by an electronic workflow that had predefined 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). SLIMS also provides full barcode support and each sample had a unique barcoded label to enable tracking; as samples are composited, mixed, or aliquoted, they can be tracked by the system individually along with their relationship to the parent sample. All analytical work was done in SLIMS (e.g., never retype data) so that the analysis progress could be found on-line with an estimate of reporting. A SLIMS Store website is where customers can download modules to expedite building workflows.

Checking laboratory resources. SLIMS can verify if an instrument is qualified or calibrated and available for use in an analysis.

Implementing analytical procedures. Pharmacopoeial monographs (left side of FIGURE 8) contain several tests used for release with acceptance criteria and any sample must select all applicable analytical procedures in SLIMS. Implementation is achieved as follows:

- A simple workflow to visualize all work is broken down to define the data to be acquired and processed.
- SLIMS modules or protocols are matched to start automating the procedure.
- A module can incorporate contemporaneous note-taking to record observations.
- Calculations can be included.
- Modules can capture data from instruments.
- CDS was interfaced to the LES to transfer data and results electronically.
- Second person review followed before release of the report.
- OOS results are highlighted.
- Data are archived within the system for the records retention period (e.g. know where the data go).

This results in the workflow on the right side of FIGURE 8: arrows represent a protocol containing the specific instructions and circles are samples pending analysis.

Case study summary. Manufacturing and QC are integrated so that sample receipt, analysis, and reporting are automated with a certificate of analysis. Customer experience is good with business benefits and plans for expansion of the system. In addition, a recent inspection was easier than in the past as records were readily available via the system.

SUMMARY

An automation strategy is essential for successful implementation of informatics solutions. Take advantage of application convergence to reduce the number of applications required. It is better for an informatics product to fit a lab rather than commit to extensive configuration or customization and involving users is critical to success when implementing a solution.