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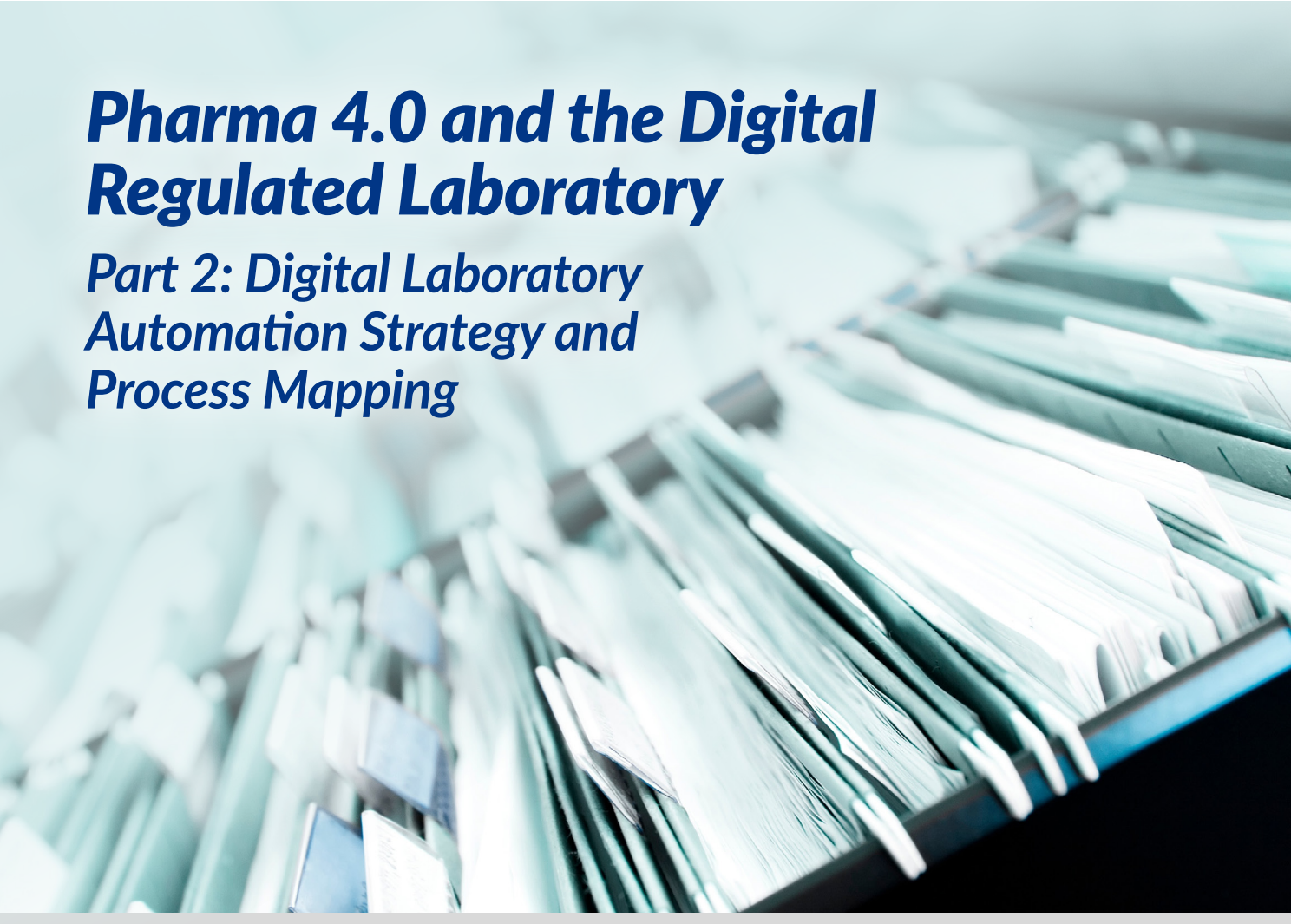
Pharma 4.0 and the Digital Regulated Laboratory

Part 2: Digital Laboratory Automation Strategy and Process Mapping



- Current Processes
- System and Instrument Assessments
- Redesigning Processes
- Planning the Digitalization Strategy

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Introduction

Let's start this second eBook on digitalization of regulated laboratories with a very blunt question: How efficient is your laboratory?

Judging from many laboratories that I have visited, consulted with and audited over the years, not very efficient is the answer. My view is reinforced by reading the warning letters and 483 observations published on the FDA's wall of shame [1]. The dreaded phrase "*you have failed*" brings a litany of examples that are the result of not modernizing a laboratory:

- Reliance on paper records
- Use of hybrid systems
- Failing to backup e-records or link e-records with the printouts
- Use of unvalidated spreadsheets
- Failure to use existing systems to their full potential
- Using instruments with capability to store electronic records but relying on printouts alone [2]

These are the citations from laboratories that are not involved in falsification and fraud. The main problem running through all these citations is the *Hidden Factory*.

The Hidden Factory in Your Laboratory

Ask any analyst what the function of a laboratory is and why they work there, and you will get one of two answers. The first may seem frivolous but true, and that is they to get to play with some amazing toys. Sorry, analytical instruments. The second is to analyze samples, interpret the data and generate results for people to make decisions as well as play with some amazing toys. What nobody will ever say is that the function of a laboratory is to generate reams of paper records.

Welcome to the Hidden Factory.

The Hidden Factory in your laboratory hides in plain sight and is all around you. There is a single product of this factory: paper.

Introduction

In many laboratories, paper constitutes most analytical records. Whilst there are electronic records generated and stored in instrument data systems, many laboratories still print paper out of custom and practice or an edict from the sadists in QA. Welcome to the nightmare world of paper and hybrid systems that make up your Hidden Factory.

Advantages of Paper Records

This is a very short section: What are the advantages of paper records?

- **Flexibility**
  A paper record is easy to establish and is infinitely flexible. If you modify a process, just redesign the associated paper form or add another sheet of paper. No messing around with software configuration and no computer validation to worry about.

- **Visible Error Correction**
  Errors are easy to correct and a reviewer does not have to wade through all those annoying audit trail entries to see them. Corrections are in plain sight, although you may have to squint to read the reason for change with some individual's handwriting.

- **Known Archive Properties**
  Paper is a relatively robust record medium with less likelihood of data loss, except when you attempt undocumented chromatography by spilling solvent on the pages. Paper has well understood archive properties if the environmental conditions are maintained and monitored.

That was quick, now we'll spend more time looking at the problems with paper.

Disadvantages of Paper Records

Unsurprisingly, there are several disadvantages of paper records:

- **Blank Forms**
  Blank forms can be at the heart of data falsification and, therefore, need to be controlled by uniquely numbering each form, allocating a form to an individual or group for use and reconciling when the work is complete as required by data integrity guidances [3-5]. For more information on how to implement controlled blank forms, see the article by Burgess and McDowall [6].

- **Administrative Costs**
  Blank forms are expensive to administer, but the cost is hidden from management as it comes from general staff payroll rather than a specific budget item. The cost of long-term record storage is expensive either with on-site buildings and associated staff or off-site storage rental costs.

- **Record Access**
  Think about your laboratory notebook. Anybody can read it when it is placed on the top of your desk. But nobody can if it is locked in a desk drawer. Look further to QC batch records from product analysis. There is only one copy of the paper record and it is difficult to share all the information with more than one person. Of course, your laboratory has never lost a batch record?

- **Limited Search Capability**
  Although there is a requirement for trending some analytical data in EU GMP Chapter 6.9 [7], this is difficult to achieve with paper. It requires that information be abstracted from paper and entered into an informatics application over time to trend results. This is a slow, tedious and error prone process. Searching through paper records to extract data for Annual Product Reviews [8] or Product Quality Reviews [9] is the same.

- **Storage**
  It is obvious that paper is a physical record medium that, in massive quantities, has bulk and weight requiring much storage space with a controlled environment. Typically, paper records are stored on site for up to two years and then transferred to an off-site records management facility until the end of the retention period when they should be formally destroyed. At the start of the off-site storage process, all records must be organized and indexed, which is manual and error prone. This is because if required for inspection, audit or complaint investigation, records must be retrieved rapidly under the service agreement with the records management company.

The Gift That Keeps on Giving

There is a bonus from the Hidden Factory: If a reviewer finds an error in any data. The paper records are returned to the analyst to correct. After the correction, guess what? Yes, some or all the corrected record set are printed again and added to the batch records, an environmentally friendly approach. The Hidden Factory is the gift that keeps on giving.

Introduction

What Needs to Be Done?

Therefore, one aim of digitalization is to demolish the Hidden Factory and replace it with automated processes with a major reduction in paper output for the records that constitute the analytical batch record. Note, I have not written paperless but with less paper. The reason is that it may not be possible to eliminate all paper records. Either it is too expensive to do so, or it is not technically feasible.

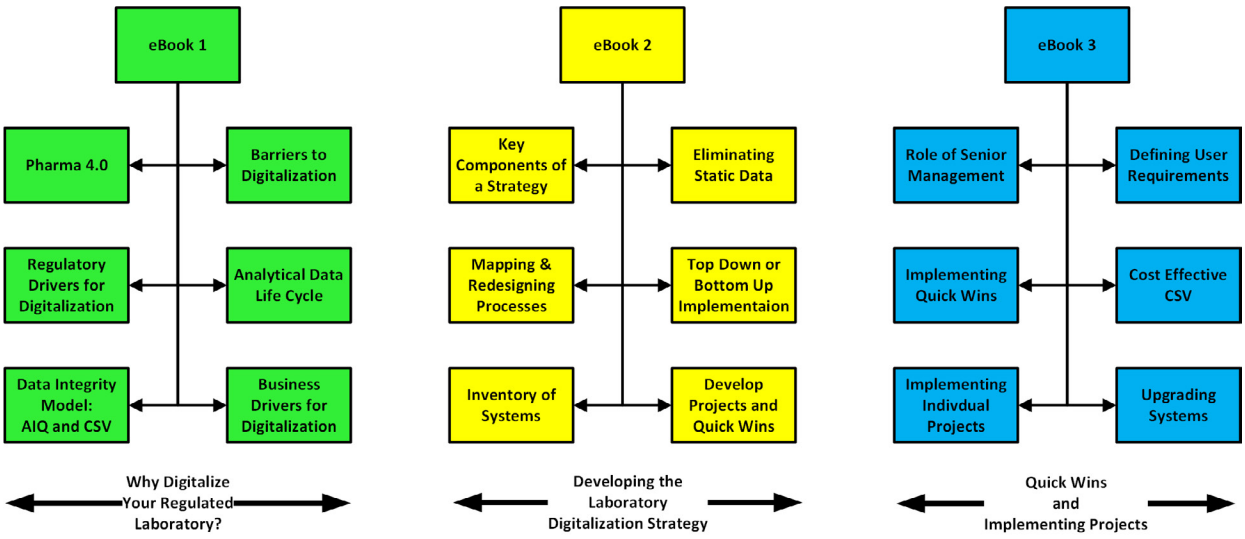
Continuing the Digitalization Journey

This is the second of three eBooks on planning and realizing a digitalized regulated laboratory (FIGURE 1). The series is aimed mainly at Good Manufacturing Practice (GMP) but the principles outlined here can also be used for laboratories working to Good Laboratory Practice (GLP). These three eBooks look at the journey from where your laboratory is now, through assessing systems and processes, planning how to automate your laboratory in stages and finally implementing quick wins and projects.

eBook 1: The Story So Far

The first eBook considered the current regulatory background, including why it is important to keep current with advances in technology, understanding the costs of compliance and non-compliance as well as some key FDA regulatory citations. Then it discussed how critical Analytical Instrument Qualification (AIQ) and Computerized System Validation (CSV) were for ensuring both regulatory compliance and data integrity. However, the approach

FIGURE 1: Overview of the contents of the three Laboratory Automation eBooks.



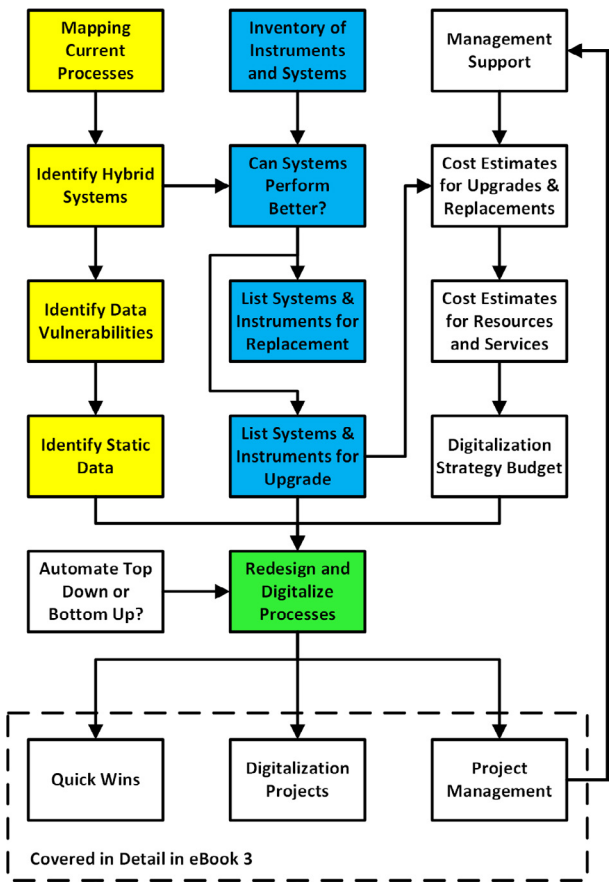
taken must be focused and risk-based, with a scientifically sound justification. Some of the barriers to digitalization discussed were spreadsheets, hybrid systems, ultra conservative nature of the pharmaceutical industry and static data. This led into a discussion on a flexible analytical data life cycle and why it is important to eliminate static data. Finally, the business drivers for digitalization and the need for a strategy for the whole laboratory is essential for management support and resourcing.

eBook 2: Digital Laboratory Automation Strategy and Process Mapping

In this eBook, the central question posed is: Where you are now and where do you want to be?

To start, we will map a laboratory's current or "*As Is*" processes. In this we need to identify bottlenecks and the problems of each process. In addition, we need an inventory of current computerized systems. We need to review how they are used now, look at their unused capabilities and determine if they can be used to automate a process. It is likely that some systems will not be capable of automating the new ways of working and need to be replaced. The three rules of laboratory automation will be described and used to digitalize a laboratory for more efficient and effective electronic working. This requires resources, both human and monetary, to be available and, hence, the role of senior management is key to supporting the approach. A laboratory automation strategy that outlines projects with timescales and resources (with contingency for both) is essential to achieve the digitalization strategy for a laboratory. The detail in this eBook can be seen in FIGURE 2.

FIGURE 2: Detailed contents of eBook 2.



Introduction

eBook 3: Quick Wins and Implementing Projects
The next eBook will discuss a laboratory automation strategy that consists of digitalization projects and quick wins.

Quick wins are small-scale improvements that can be implemented relatively quickly and inexpensively with some business benefits. These should be started first, as they give credibility and visibility to the overall automation strategy. It is crucial that senior management encourages the strategy from the first quick win implementations onwards.

Digitalization projects are larger, requiring more time and resources to implement, but with the potential to return bigger business benefits. The first digitalization project is critical to the success of the laboratory and credibility of the strategy. This requires not only project risk, but regulatory and implementation risk to be minimized to ensure success. Simpler and easier projects here with no custom software developments are candidates to ensure success. Validation is a critical requirement in a regulated laboratory, but too often companies take a conservative approach that delays a project. We need to leverage a supplier's software development, manage risk and apply sound science to focus scarce resources to where they are most needed.

As the strategy progresses, new technologies may emerge requiring a revision of the overall strategy after implementation of a major system, or every 12-18 months. This is normal and should be expected.

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1. *FDA Warning Letters*. Available from: http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm.
2. *FDA Warning Letter BBC Group Limited*. 2021; Available from: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/bbc-group-limited-614659-08042021.
3. *FDA Guidance for Industry Data Integrity and Compliance With Drug CGMP Questions and Answers* 2018, Food and Drug Administration: Silver Spring, MD.
4. *WHO Technical Report Series No.996 Annex 5 Guidance on Good Data and Records Management Practices*. 2016, World Health Organisation: Geneva.
5. *PIC/S PI-041 Good Practices for Data Management and Integrity in Regulated GMP / GDP Environments Draft*. 2021, Pharmaceutical Inspection Convention / Pharmaceutical Inspection Cooperation Scheme: Geneva.
6. Burgess, C. and R.D. McDowall, *Paper, Paper Everywhere but None of it Controlled*. LCGC Europe, 2016. **29**(9): p. 498 - 504.

7. *EudraLex - Volume 4 Good Manufacturing Practice (GMP) Guidelines, Chapter 6 Quality Control*. 2014, European Commission: Brussels.
8. *21 CFR 211 Current Good Manufacturing Practice for Finished Pharmaceutical Products*. 2008, Food and Drug Administration: Sliver Spring, MD.
9. *EudraLex - Volume 4 Good Manufacturing Practice (GMP) Guidelines, Chapter 1 Pharmaceutical Quality System*. 2013, European Commission: Brussels.

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Where Are You Now?
Understanding Your Current Processes

Most laboratory processes have evolved over time. Changes in working practices can come from a change in laboratory management (ie, "I'm in charge now and this is the way we work."), Quality Assurance interpretation of regulations as well as audit or inspection findings. As noted earlier, a paper process just needs to generate a new form and the problem is solved. This also creates legacies that newer personnel may not be able to explain without complete and thorough documentation. However, a paper approach just compounds the problem of process inefficiency and increased overhead to ensure data integrity and regulatory compliance.

PRE-REQUISITES FOR AUTOMATION

As discussed at the end of the first eBook, automating a complete laboratory is not a quick fix and requires the following pre-requisites

incorporated into your overall laboratory digitalization approach:

- Active management support (this subject will be discussed in the third eBook)
- Resources (both staff and money)
- Process mapping and redesign
- Interpretation of regulatory requirements and effective risk management
- Identifying and solving data integrity vulnerabilities
- Strategic planning for the whole laboratory coupled with quick wins coupled with individual project planning for implementation of specific applications
- Focused computer validation that leverages supplier development to reduce in-house effort
- Active user involvement and training
- Quality oversight from staff with IT knowledge

If a laboratory is going to be digitalized, a structured approach must be used. The first part is to understand where you are now. As shown on the left-hand column of FIGURE 1, this will involve:

- Mapping your current processes
- Identifying where hybrid systems are used
- Identifying any data vulnerabilities
- Identifying static data

Let us begin with finding out how you **actually** work.

MAPPING CURRENT PROCESSES

In an ideal world, we would not need to do anything except read current SOPs, work instructions and analytical procedures to understand how you work. This is your *As Intended* process.

Unfortunately, it is not an ideal world and many written instructions are often major works of artistic fiction or have Grand Canyon-sized gaps in them. Therefore, we need to map the process to find out your *As Is* working practices. The question is, how do we do this?

FIGURE 1: Detailed Contents of eBook 2.

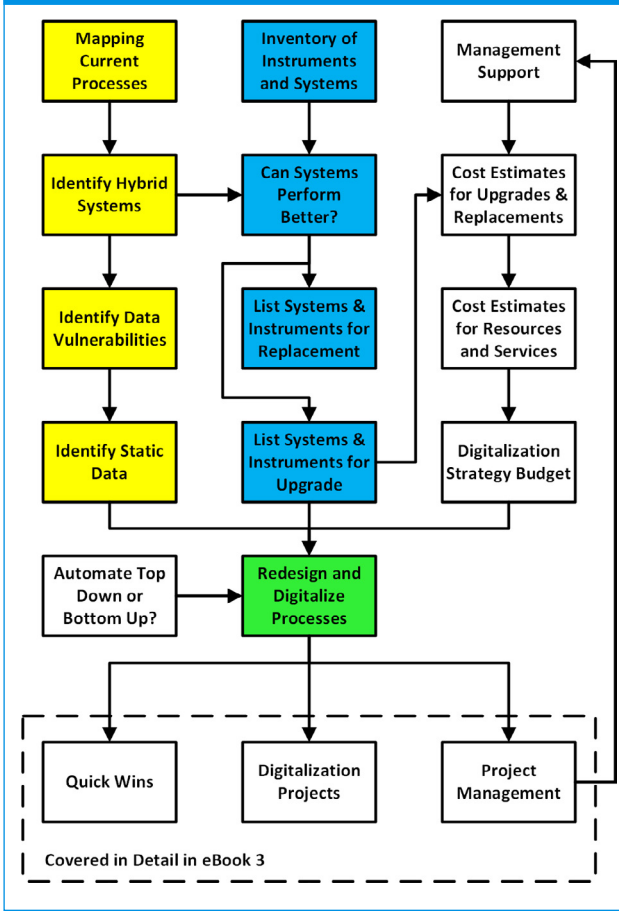
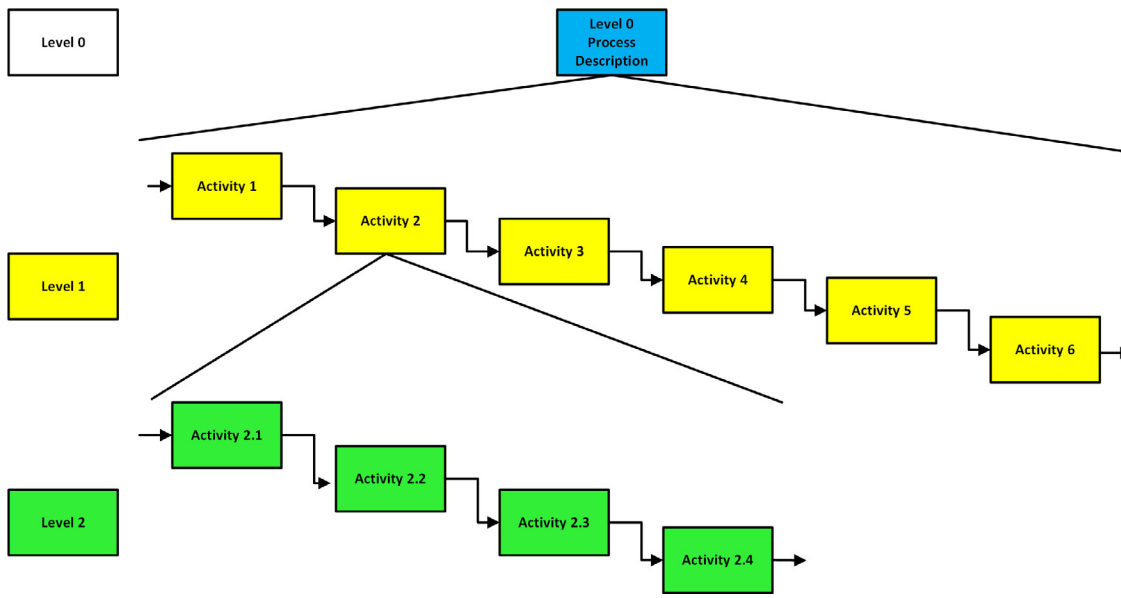


FIGURE 2: IDEF Process Mapping - A Logical Decomposition of a Process.



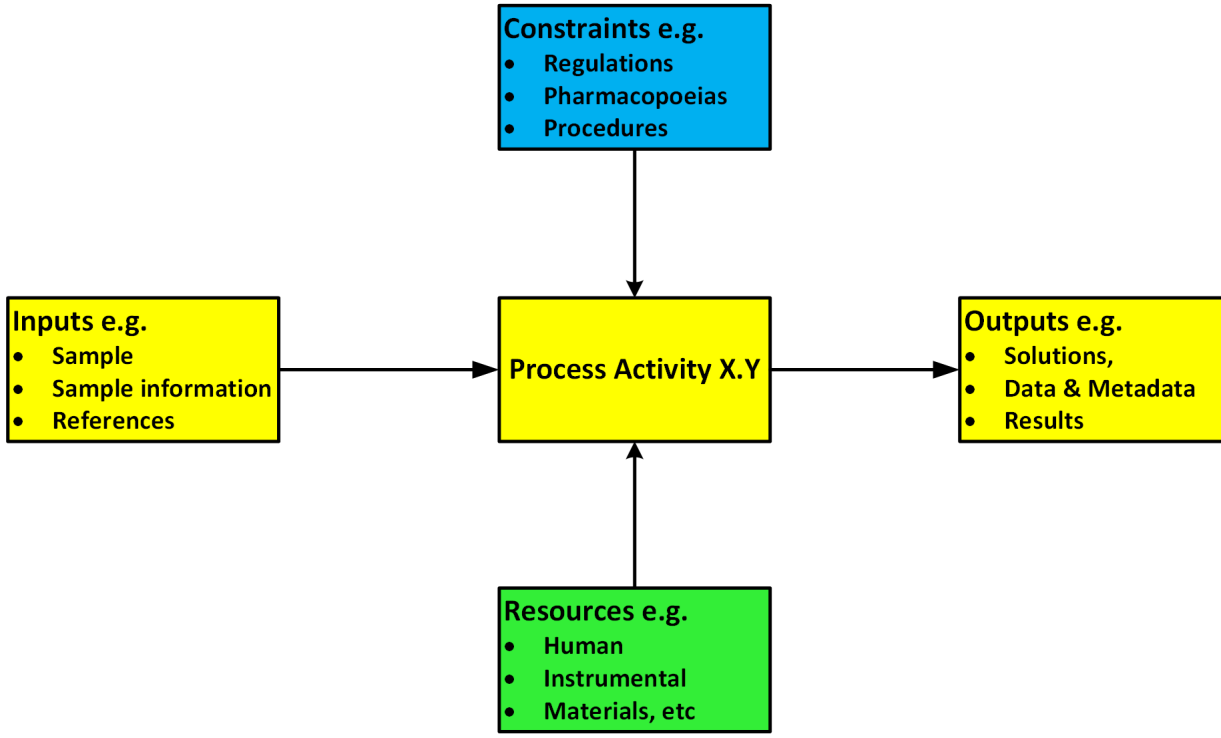
IDEF Process Mapping Methodology

The main process mapping methodology that I have used for nearly 30 years is called IDEF, or Integrated Definition. It is a logical process of decomposing a process from the top-down process definition at Level 0, into a high-level primary process at Level 1 and into more detail at Level 2, as shown in FIGURE 2.

The approach is a logical top-down decomposition of a process as follows:

- **Level 0 Process Description**
  Define the process and its boundaries along with the inputs, outputs, resources required and any constraints
- **Level 1 Process Definition**
  This is a definition of the primary process where the description is broken down into between **6 and 12 main activities.** FIGURE 2 shows six activities for simplicity. It is important not to cram every laboratory activity into this level, as there are many supporting processes such as instrument maintenance/ qualification, standards management, method validation, stability testing, etc. Separate processes require separate process maps with identification of how each process interacts with another.
- **Level 2 Further Decomposition**
  Each activity at Level 1 this is broken down further into between 4 and 8 activities. Although it is possible to create further levels, it is not necessary. Sufficient process information can be obtained by Level 2 to see where there are problems and bottlenecks in the process.

FIGURE 3: IDEF Activity Inputs, Outputs, Resources and Constraints.



In my experience, further detail below Level 2 is only required if two systems are being interfaced. This helps define how and when data are transferred between the two systems.

At this stage, we have an outline of the process but need the detail of what is required. We find this in FIGURE 3. The process activity is shown in the center of the figure, there are inputs to the left and after the activity is complete there are outputs described on the right-hand side. These are the key elements required for all activities in the IDEF map.

Also shown in FIGURE 3 are the business and regulatory constraints on the activity. These must be described at Level 0 but only where necessary on each activity. It is unnecessary to write GMP as a constraint for each activity. Only input a constraint where necessary to understand the activity. The other items in FIGURE 3 are the resources required for the activity. A similar approach will be taken here as well.

MAPPING A PROCESS

This should be performed in a quiet location, away from phone calls and e-mails, where a facilitator and subject

matter experts from the laboratory and, where appropriate, IT and QA can work undisturbed. That's the theory anyway. The reality is sometimes different.

"What should also be collected at the end of the workshop are improvement ideas from the attendees. These are the people who are involved with the process daily."

Using either a white board and markers or large flip chart paper with sticky notes and pencils, the process will be described and defined. The reason for using pencils is that any mapping process is iterative as you expect mistakes or omissions to be made. Rubbing out pencil lines connecting the activities is easier that using a pen. Yes, I know this is not compliant with GMP but there are no regulatory records involved. Don't forget to have some sticky tape to ensure that the sticky notes don't fall off the pages. It can get very embarrassing for the facilitator otherwise.

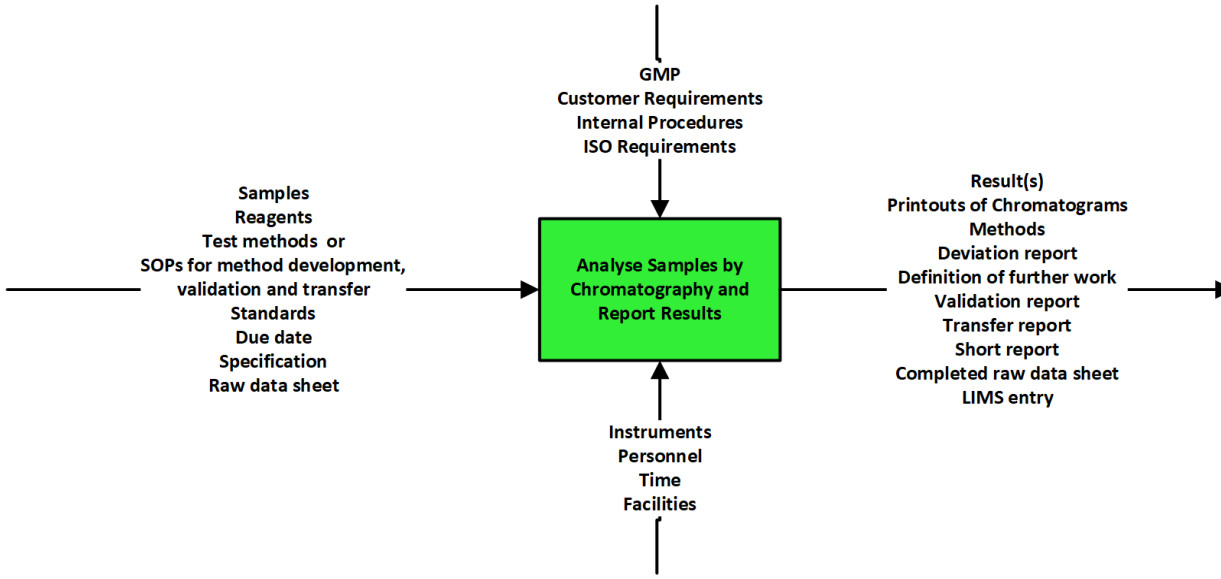
If you have the technology available, an alternative can be the use of a virtual board with virtual sticky notes. Personally, the physical approach is faster for mapping but slower when converting the physical notes into an electronic diagram.

What should also be collected at the end of the workshop are improvement ideas from the attendees. These are the people who are involved with the process daily. They have ideas for improvement. Improvement ideas should be linked to specific activities within the *As Is* process maps.

Regardless of the mapping approach, the IDEF process maps need to be drawn up and input into an *As Is* report. An application that is useful for drawing the process maps is Visio®. Personally, I don't use the IDEF stencils in the application, as the standard flow chart stencil provides greater flexibility in drawing. Regardless, the maps are copied and pasted into the report of the *As Is* mapping workshop. Then the associated inputs, outputs, sources and constraints are added to the draft report for review by the attendees. Expect corrections to the maps. Although everyone will agree at the end of the workshop, the cold light of day results in increased objectivity and corrections are inevitable. Regardless of the mapping approach, we will use the process maps as inputs when we redesign the process in the later article, **Where Do You Want to Be? Redesigning Processes.**

"Expect corrections to the map. Although everyone will agree at the end of the workshop, the cold light of day results in increased objectivity and corrections are inevitable."

FIGURE 4: *As Is* Level 0 Process Description.



Case Study Example: Level 0 Process Description

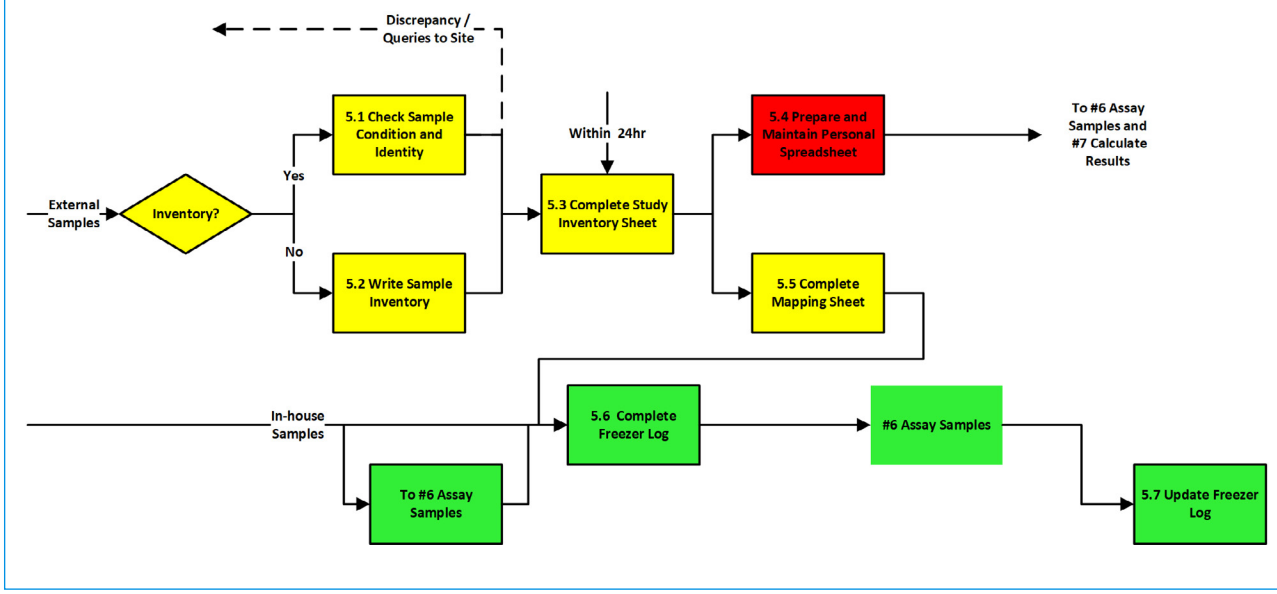
A case study example of a Level 0 process description for chromatographic analysis is shown in FIGURE 4. The content looks relatively simple and easy to develop, however it takes time to get attendees who are new to process mapping used to doing it. This one diagram took nearly an hour to develop, with a facilitator encouraging and challenging the attendees. Once the understanding of IDEF mapping is gained, the process mapping goes much faster.

Case Study Example: *As Is* Sample Management Process

FIGURE 5 shows a case study sample receipt and management ***As Is*** process at Level 2 of the process decomposition. You will notice the following features:

- A straightforward process (in green) for samples generated in-house where samples can either be analyzed on receipt or logged and frozen prior to later analysis.
- There is a more complex process (in yellow) for samples arriving from external sources. An inventory is either submitted electronically or the laboratory must generate one.
- Activity 5.7 has a constraint of completing an inventory and logging samples within 24 hours. This was mandated by management after the laboratory lost a batch of external samples.
- A paper freezer logbook is maintained for all samples.
- In addition to the formal processes described above, there is an unofficial

FIGURE 5: An *As Is* Process Map of Sample Receipt and Management.



process (in red) that one individual uses, as it is simpler and easier than the formal processes.

PROCESS ANALYSIS: YOU CAN'T AUTOMATE A MESS

The process described in FIGURE 5 has several "features":

- **Three sub processes:** two formalised in SOPs and one uncontrolled, undocumented and non-compliant
- **Paper records:** sample inventories and the freezer logbook
- **Activity 5.7, a management-mandated activity:** drop everything, inventory and log external samples within 24 hours. This point illustrates the incremental evolution of a process rather than the design of one.

Now we come back to the question posed at the start of this eBook: How efficient is your laboratory?

Many readers may be tempted to take the Fifth rather than answer this question. However, consider an alternative question: How would you digitalize this portion of an analytical process? The simple answer is that you cannot easily do so. Moreover, automating three processes is inefficient, and validating them will cost much more compared to a single integrated process.

Case Study Example: *As Is* Process - Identifying Hybrid System Use

Moving on from sample receipt and management, let us consider an end-to-end chromatographic analysis, from sample management to reporting results shown in

FIGURE 6: Chromatographic Analysis and Hybrid Records.

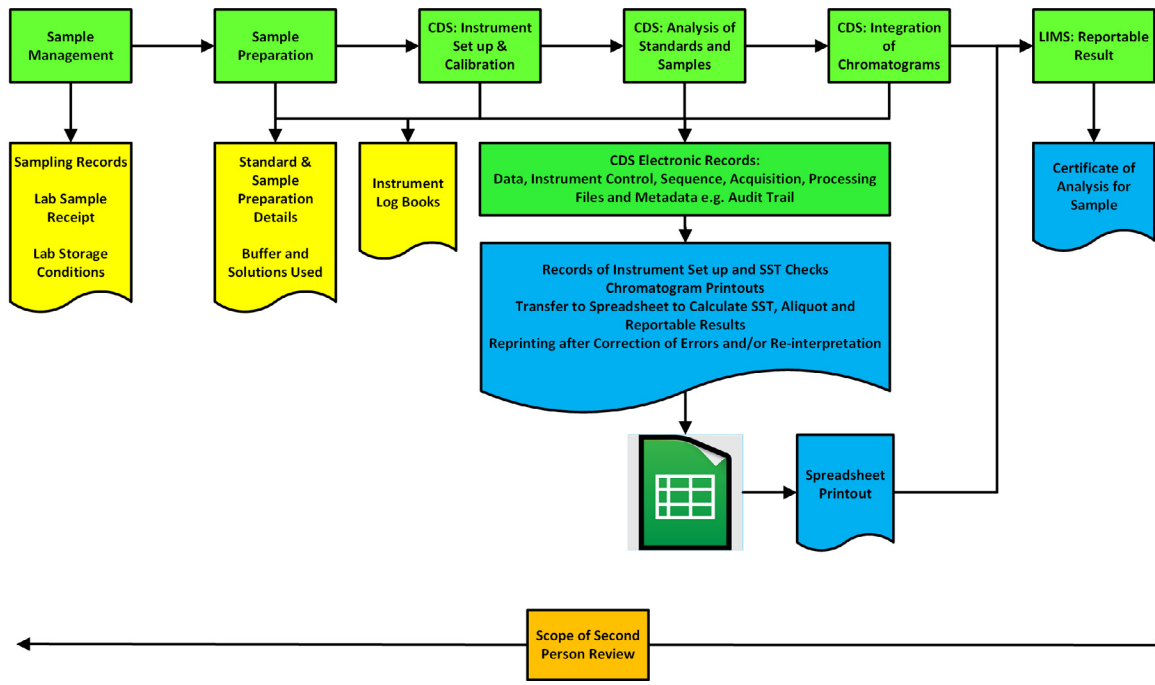


FIGURE 6. The overall process is shown in green, along with the electronic records from the CDS. However, the process is slow and inefficient, as we can see now.

- Sample receipt and management is paper based
- Refrigerated and frozen storage cabinets are monitored using chart recorders
- Sample preparation records including instrument printouts from balances and pH meters and the associated logbooks are all paper records
- Sample information must be entered manually into the CDS
- There are three hybrid systems in the process: CDS used as an electronic ruler to integrate peaks then chromatograms are printed out, peak area are typed into a spreadsheet to calculate the SST parameters and reportable results which are printed out and the results from the spreadsheet are manually entered into the LIMS for generating the Certificate of Analysis.

That is just the analyst performing the work. Now think of the poor second person who must review this mess of records. Piles of paper, matching electronic records with printouts and multiple transcription error checks. Is it any wonder that the review takes longer than the analysis in many cases?

As Is Process: Identifying Data Vulnerabilities

Where to start when considering the data vulnerabilities in FIGURE 6? Let us focus on the three hybrid systems and the way they are used. For reasons of space, we will not consider any data vulnerabilities within in the LIMS or CDS themselves, such as protection of records or conflicts of interest for user roles.

- **CDS**
  Electronic records and paper printouts. The functionality of the CDS is not used to the full extent. It is only used to acquire data and integrate peaks to generate peak areas. All calculations that are performed by the spreadsheet can be done by the CDS, but that is ignored by the chromatographers in the laboratory.
- **Spreadsheet**
  The major data vulnerability is with the spreadsheet. There is manual entry of peak areas, sample information, sample weights and reference standard weights, purities, water content etc. This is an error-prone process. Checking during the review process may find errors that have to be returned to the analyst to correct. All could be avoided if the calculations were incorporated into the CDS.
- **LIMS**
  Manual entry of the result is a potential data vulnerability, as it must be carefully checked to ensure the right result is associated with the right sample and that no transcription errors have occurred.

Again, elimination of hybrid systems should be a priority.

"It is critical to have a baseline measurement of how well or poorly the current process is performing. For this you need to generate meaningful metrics."

METRICS OF THE CURRENT PROCESS

It is critical to have a baseline measurement of how well or poorly the current process is performing. For this, you need to generate meaningful metrics. Some organizations do this already (e.g. a key performance indicator (KPI) for many laboratories is turnaround time [TAT]). This is defined as the time taken from sample receipt to the issue of the Certificate of Analysis. There will be a target time and metrics should show the number of samples analysed within this time as well as those outside it. This can be coupled with the number of samples submitted from the laboratory. Other metrics may also be useful. Newton and McDowall have published an article on metrics from the perspective of data integrity, but some metrics may also be useful as means of monitoring laboratory performance [1].

The aim of the metrics is to benchmark the current laboratory performance. Turnaround time can be broken down using the *As Is* process maps, especially Level 1. There, the overall time can be shown across the whole process, and an estimate for each activity in the process given. When the To Be process is designed, time estimates can be used to see how much resource is saved and, hence, quantified into saving for the organization.

Care needs to be taken, as this is not a resource-saving exercise. Support for the new systems from existing staff will be necessary. This is discussed later in eBook 3.

Now we need to consider an assessment of the current analytical instruments and computerized systems in the laboratory.

References:

1. M.E.Newton, R.D.McDowall., *Data Integrity Metrics for Chromatography.* LCGC Europe, 2017. **30**(12): p. 679–685.

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Where Are You Now?

Current System and Instrument Assessments

This phase of the digitalization strategy development can be undertaken in parallel with the process mapping and redesign, or it can be performed before or after. My preference would be to do it before so it can be an input to the process redesign phase discussed later in Where Do You Want to Be? Redesigning Processes.

AN UNUSUAL REGULATORY GUIDANCE

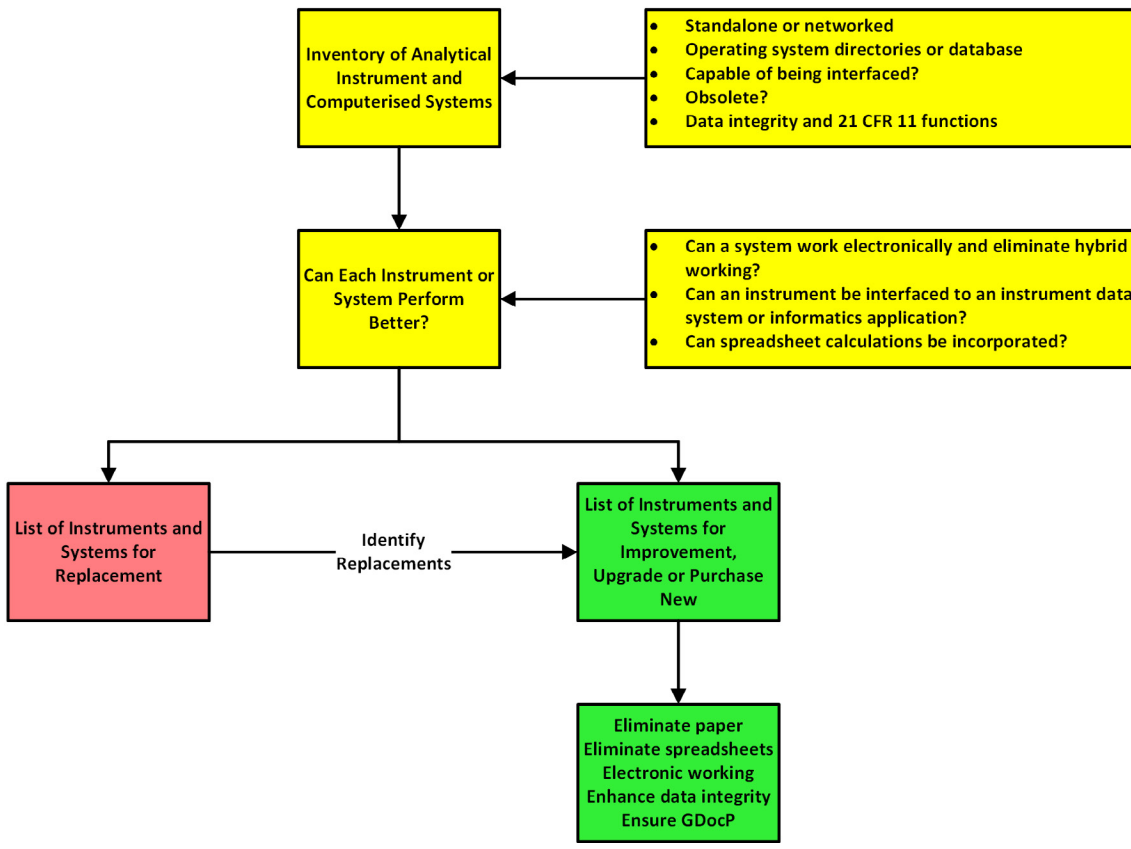
Why are we doing an assessment of current computerized system and analytical instruments?

In "Business Drivers for Digitalization," eBook 1, we looked at section 5.6 from the 2016 WHO guidance:

> *§5.6 A data management programme developed and implemented upon the basis of sound QRM principles is expected* ***to leverage existing technologies to their full potential.***
>
> *This in turn will* ***streamline data processes*** *in a manner that not only* ***improves data management*** *but also the* ***business process efficiency and effectiveness,*** *thereby* ***reducing costs*** *and* ***facilitating continual improvement*** *[1]*

See eBook 1 for a detailed discussion of the highlighted phrases for a regulatory guidance document encouraging streamlining of data processes, improving business efficiencies and reducing cost. Now we begin to put this guidance into practice. The overall process is shown in FIGURE 1.

FIGURE 1: Assessment of Computerised Systems and Analytical Instruments.



INVENTORY OF COMPUTERIZED SYSTEMS AND ANALYTICAL INSTRUMENTS

Our starting point for this segment of the strategy is your inventory of computerized systems and analytical instruments. You have got an inventory, haven't you? As a hint, it is a specific requirement of clause 4.3 of EU GMP Annex 11 [2].

Normally the inventory will list each computerized system, including spreadsheets and analytical instruments, with the status, GMP impact, etc. This is our input to the assessment process, as shown in FIGURE 1.

This is where you will find out if your laboratory is an extension of the local science museum or not. It will also bring home to management that failing to keep current will cost more to digitalize than if they had invested properly in systems and instrumentation.

Analytical Instruments

Each analytical instrument in the inventory will have the make and model number listed. This needs to be expanded with the following information:

- **Data Output**
  How are data output from the instrument? By observation or by printer? Analytical balances without a printer should not be used and should be replaced immediately. The data integrity risks are too critical to consider any other action.
- **Instrument Reliability**
  How well does each instrument perform, and is each instrument reliable? If there is a history of faults, is this due to the use and maintenance in the laboratory or other factors?
- **Interface Capability**
  This is important, as instruments that have no interfacing capability are of little use in a digitalized laboratory and should be listed for replacement immediately.
- **Obsolete or Obsolescent**
  Even if there is interface capability, is the instrument going to be supported for the medium term of 5 years? Or are there plans for replacement by the supplier? Age is also a determining factor, as any interface capability may be obsolete or becoming so.
- **Supplier Support**
  Experience with a supplier can determine if you want to continue to work with them or if they are problematic from the perspective of support and service.

Computerized Systems

A similar approach needs to be taken with computerized systems, both those controlling an instrument and applications on their own. We will deal with spreadsheets separately, in the next section.

Instrument data systems must have information on the instrument controlled by the application plus the following:

- **Standalone or Networked**
  Data stored on a standalone PC in the laboratory has major data vulnerability, as a failure can result in data loss. When a laboratory is responsible for backup, it is in second place to doing the work and may not get done, as seen in the Ohm Laboratories warning letter [3]. Acquisition of data directly to the network is the preferred solution.
- **Hybrid System**
  As mentioned in the first eBook, hybrid systems are the worst possible option, as there are two incompatible record formats to synchronize and manage throughout the record retention period. As both the PIC/S and WHO guidances make clear, hybrid systems are not encouraged and replacement of hybrid systems should be a priority [1,4].
- **Platform**
  Which operating system version is being used to run the application? Pharmaceutical companies commonly take the approach of, **if a system is validated, don't touch it!** Consequently, many systems run on obsolete and vulnerable operating systems. These need to be identified. Obsolete or obsolescent operating systems may result in the IT department refusing to connect such systems to the network, or securing them in isolated networks leaving the laboratory to back up data and open to regulatory citations [3].
- **Architecture**
  How are data stored by the system? In directories in the operating system or in a database? The former option results in the opportunity of users to delete data outside of the application and its audit trail. This can require the IT Department to spend time securing the operating system.
- **Obsolete or Obsolescent**
  How old is the application, and is it still supported by the supplier? Some suppliers will only support obsolete systems by providing patches for known software bugs.
- **Data Integrity Assessment**
  The assessment for the digitalization strategy should also be linked with the data integrity assessment already performed on the system. You have done this assessment, right?

This information is crucial for the next stage of the assessment process.

"Your inventory must include a listing of all spreadsheets used in the laboratory and their validation status."

Spreadsheets: Function and Calculation
Your inventory must include a listing of all spreadsheets used in the laboratory and their validation status. In addition, look at the following:

- **Spreadsheet Use**
  If not listed in the inventory, provide detail of how the spreadsheet is used in the laboratory.

- **Data Input**
  How are data entered into the spreadsheet? Manually or via a csv file output from an application and imported into the spreadsheet?
- **Calculations Performed**
  List the calculations performed by the spreadsheet.
- **File Saving**
  Is the spreadsheet file saved after data entry? If not, this is a failure to ensure that complete data are retained under 21 CFR 211.194(a) [5] and the FDA Data Integrity Guidance question 12 [6].
- **Record Signature Linking**
  As required by 21 CFR 11.70 [7], the signed paper printout must be linked with the electronic record that generated it. Does each spreadsheet meet this requirement?

CASE STUDY EXAMPLES: CAN SYSTEMS PERFORM BETTER?

One of the corollaries of Murphy's Law is Cahn's Axiom: *When all else fails, read the manual*. We will now put this into action to identify if existing applications have functionality to meet the WHO requirement *to leverage existing technologies to their full potential* [1]. Some questions to pose here are:

- What unused functions can be used to eliminate paper?
- Can a system work electronically and eliminate hybrid working?
- Can an instrument be interfaced to an instrument data system or informatics application to ensure integrity of capture and eliminate static data printouts?
- Can spreadsheet calculations be incorporated into another application, and the spreadsheet eliminated?

You may think that laboratories already use their analytical instruments to their full potential. This is not so. Let me provide you with three case study examples of a simplistic use of systems based on recent consulting and auditing projects in GMP-regulated laboratories:

CASE STUDY 1: Fully Automated Dissolution Testing

A fully automated dissolution system consisting of dissolution bath, sipper system to automatically transfer vessel fluid to a UV spectrophotometer system and used to calculate the percentage dissolution is used for 49 different methods. BUT…

- Only one method uses the full capability of the system where the operator drops a capsule into each dissolution vessel, and then reviews the calculated results at the end of the experiment and prints the results.
- There is also electronic signature capability, but that is a minor distraction from the disaster that will now unfold.
- The remaining 48 methods use the system manually. An analyst drops the capsules into the vessels at two-minute intervals. Sampling from the vessels is manual, and fluid is pipetted manually into cuvettes and read in the spectrophotometer. The readings are then input into a spreadsheet for calculation of the percentage dissolution. Can you believe this?!

CASE STUDY 2: Identity Testing by Fourier Transform Infra-Red (FT-IR)

Two different laboratories in two different organizations use two different FT-IR systems for identity testing of incoming active pharmaceutical ingredients (API). However, they use each system the same way: badly.

- Sample spectra are obtained, printed out and compared with reference spectra printouts. In both cases, the printouts of all spectra must be signed and dated.
- Objective criteria for confirmation of identification are missing in action and it is left to the judgement of the analyst of the day to determine if the sample and reference spectra are the same. There are no details in the SOP or analytical procedure, and comparison is very subjective. This is an auditor's or inspector's fun fest.
- Both applications have a Compare function. A reference spectrum is captured and the wavenumbers of 4 – 6 key peaks for identification are listed in the compare function for the compound. A sample spectrum is compared with the reference key peaks and the system automatically determines if the identity is correct or not. Simple! Only one piece of paper to be printed, the spectra remain in the spectrometer.
- But wait, there is more. Both systems have electronic signature capability. If electronic signature capability were implemented, you could eliminate paper.

Given extent of regulatory attention given by inspectors to Chromatography Data Systems (CDS) since the Able Laboratories fraud case [8], you could be forgiven for assuming that there would be few problems associated with these systems. However, that assumption is wrong, as we shall see in the last case study.

CASE STUDY 3: CASE STUDY 1: Chromatographic Analysis

As was stated earlier in this eBook, the laboratory uses the CDS as an electronic ruler just to integrate peaks and calculate peak areas. The chromatograms and peak tables are printed out and the peak areas and sample weights and other factors such as standard purity and water content are input into a spreadsheet (unvalidated, naturally) to calculate SST parameters against acceptance criteria and the reportable results.

- This approach makes the post run analysis slow, error prone and a GMP compliance nightmare.
- Review by a second person takes more time to match print outs from one system with inputs to another. Correction of those typographical errors found takes time and generates yet more paper.
- Shockingly, the CDS calculates any SST parameter automatically for each injection, so the laboratory does not even have to print the SST chromatograms and enter the results into the spreadsheet!
- Reading the manual or looking at the supplier's web site or on-line videos can enable calculation of aliquot injections and averaging of the results to generate the reportable result for the sample. This would eliminate the spreadsheet and the associated printout.
- More amazingly, the system has electronic signature capability for which paper can be eliminated entirely.

Using these three case studies, you can see what can be achieved with existing systems and exiting functionality. You need to follow Cahn's Axiom and read the manual to discover what can be achieved with software you already have.

However, there are other issues for second person review to consider:

- How can audit trail review be simplified? Can changes to data be identified by the system?
- If there are no changes to data can we use review by exception to avoid audit trail review, as suggested by the PIC/S guidance on data integrity [4]?
- No user should have deletion privileges. This means that a review does not have to look for deleted data.
- Can an application enforce working practices and have only one location where data can be stored?

It may be that an older version of an application installed in your laboratory does not have all functions needed for a digitalized laboratory, but the currently released version does. Therefore, you should seriously consider upgrading the application, as you will gain the business benefits and process efficiencies.
There are two outcomes from this assessment process:

- Systems and instruments for replacement.
- Systems that will use existing functionality to digitalize a process further as well as systems and instruments for upgrading or purchase new which, when implemented, will deliver digitalization benefits.

LIST ANALYTICAL INSTRUMENTS AND COMPUTERIZED SYSTEMS FOR REPLACEMENT

One outcome of the assessment process will be a list of computerized systems and analytical instruments that must be replaced for the reasons identified in the assessment.

Budgetary constraints and resources to learn how to use the replacement items will prevent a mass replacement, so the process must be phased over time. Cost estimates for purchase of new instruments and systems along with the associated professional services (e.g., qualification, training, validation as necessary) will be an essential input covered in the next article, **Where Do You Want to Be? Redesigning Processes.**

Prioritize the replacements and, where appropriate, synchronize purchase with the process improvement projects discussed in this eBook and in eBook 3.

List of Analytical Instruments and Computerized Systems for Upgrade

An output from the assessment will be a list of the following:

- Analytical instruments to be interfaced with informatics applications.
- Computerized systems that will use existing but additional functionality.

Although software does not have to be purchased, using new functionality will require that the system undergo revalidation. The extent of this needs to be determined on a case-by-case basis.

- Computerized systems that need to be upgraded with new software if the existing version is either out of support or does not have the required functionality for digitalization. Similarly, revalidation is required, but updating existing documentation is the best approach here.
- Budget estimates are required, as described in the previous section.

We will return to this list of analytical instruments and computerized systems in the later article, **Planning the Digitalization Strategy**, discussing budgets and management support for the digitalization strategy.

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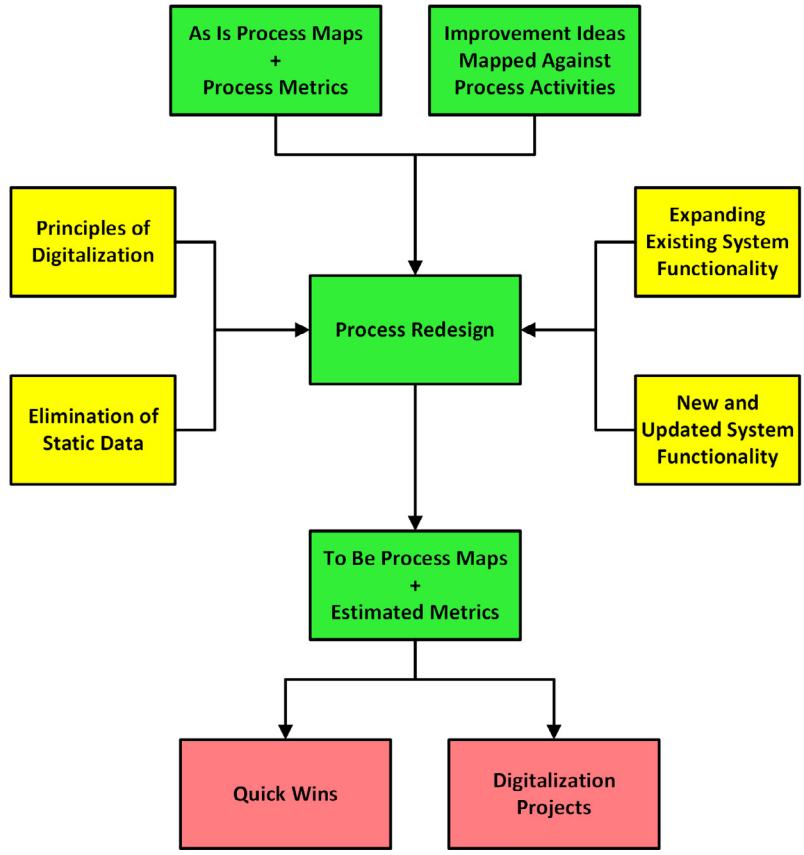
Where Do You Want to Be?
Redesigning Processes

The starting point for this chapter is the *As Is* process maps, laboratory metrics and improvement ideas from the earlier article, Where Are You Now? Understanding Your Current Processes, that will be used to redesign the process.

Note the use of the word "redesign". In the 1990s, there was a great emphasis on reengineering an organization resulting in major changes in the ways of working with staff downsizing. It is not the intention to completely change the way a laboratory operates, as we are a regulated industry and must work in compliance with the regulations, applicable pharmacopeial general chapters and guidance documents. In addition, digitalized laboratories will need lab administrators to support these new systems, so redistribution of staff is required. We will discuss this in eBook 3.

FIGURE 1: Inputs to a Process Redesign Workshop.



DESIGNING THE *TO BE* PROCESS

The overall approach to redesigning a process that we will discuss in this article is shown in FIGURE 1. The inputs on the right, in yellow, were discussed in the previous article, so we will limit our discussion to the two inputs on the left before we discuss the process redesign, itself.

The major input to a second workshop is the draft report of the *As Is* workshop, and the first stage is to correct any mistakes in the process maps. As these are now electronic, this can be achieved interactively by projecting each one on a screen and updating each map. Using the updated *As Is* process maps, users may see:

- Prioritized improvement ideas gathered at the end of the first workshop.
- Knowledge of current systems, their potential to work electronically, and the elimination of paper printouts.
- Avoidance of generating static data that later becomes dynamic, as discussed in eBook 1.

It is essential that the attendees who are laboratory users are fully engaged, as recommendations provided by word-of-mouth communication after the workshop will help spread the word about the development of the overall strategy.

There is no point to having the best digitalized laboratory in the world if the users don't use it. Technology is only part of the solution – winning and keeping the hearts and minds of the users is equally important. We shall discuss this more in eBook 3.

Once the redesigned process maps and estimated metrics have been developed, quick wins and a portfolio of digitalization projects will be the outcome. All will be written up in an expanded process redesign report containing *As Is* and *To Be* process maps, and the outlines of Quick Wins and Improvement Projects. The latter two items will be discussed briefly in this eBook and in more detail in the third eBook of this series.

Warning – Ensure Business Benefits Accrue When Implementing Systems

There is no point to implementing any computerized system unless tangible business benefits are generated.

Too much money and resources have been wasted on projects that may provide enhanced regulatory compliance but no business benefit. First, focus on delivering business benefit. Then, consider what compliance needs are required as well as what data vulnerabilities there are and resolve them. The subtitle of the first edition of my book on Validation of Chromatography Data Systems was Meeting Business and Regulatory Requirements [1]. Please note the order: business benefits come first. The second edition put data integrity before business benefits, but that was marketing – sorry [2].

I'm a User – What's in it For Me?

This is especially important to consider, and actively involves the user population in the digitalization process. You need to convince users of the benefits of any updated or new analytical instruments or computerized systems. If users perceive there is benefit for them, they will embrace the system. If it requires additional work to use the system over and above the current process, the user will be reluctant to use the new system. Never promise that users will be able to work at the click of a mouse, as this does not happen. In a laboratory you must prepare samples, maintain instruments, etc., which are not mouse click activities.

THREE PRINCIPLES OF DIGITALIZATION

When redesigning any process to work electronically, there are three principles of digitalization that must be used [3]. These are:

- Data capture at point of origin
- Never ever retype data
- Know where the data will go

We will discuss each in turn now.

Capture Data at the Point of Origin

If you are going to work electronically the data must be electronic from the start, when it is first generated or observed. Never write down data on official media or your lab coat sleeve. As we saw in the first eBook when discussing the analytical data life cycle, there is a wide range of data types that include:

- Observational data (e.g., odor, appearance, color): These are static data, as the analyst writes the result directly into a batch record or laboratory notebook. Capturing these observations directly into an informatics application provides not only the benefit of digitalization but also ensures ALCOA principles are met (e.g., contemporaneous, traceable and attributable [4]).
- Instrument data (e.g., pH, balance): Avoid printers that generate static data that later become dynamic data, as shown in eBook 1. Instead, capture the data electronically, as shown in **FIGURE 2** and discussed later.
- Electronic records are generated from laboratory informatics applications such as chromatography or spectroscopy data systems, but are these used as hybrid systems?

All must be included in the digitalization strategy, as the main aim is to capture data from whatever electronic source is available at the point of origin.

Never Ever Retype Data

The second principle is to ensure that once data are captured electronically they are never printed and re-entered manually into another computer system. Are spreadsheets performing calculations that an instrument data system can perform if users read the manual?

All data transfers must be electronic using validated processes with appropriate checks (e.g., audit trails, checksums for file integrity) to ensure that data are not corrupted. Ideally, only networked systems should be used to minimize data loss and for sharing data and information effectively. As a corollary to this principle, raw data must be defined as electronic records. Paper should only be a by-product of an electronic process used for information not defined as raw data [5] or complete data [6]. The electronic records produced in these workflows should be designated as records or raw data for archiving purposes.

Interfacing systems and applications should be a major goal, but this must be balanced with a cost-effective approach. For example, are the sample numbers and volumes sufficient to justify the cost and validation of interfacing?

Know Where the Data Will Go

Data storage repositories need to be designed for the digitalized regulated laboratory and may be distributed across several applications (e.g., LIMS, CDS, an

LES or simply secure network drives). To help size the storage, an estimate of the data volumes will be necessary. In addition, a predetermined plan of how data will be stored (e.g., by study number, drug project or product, etc.) must be developed before the repositories are implemented. This data storage plan will also include any file naming conventions for data to ensure that an individual file, analytical run or study can be retrieved quickly and with minimum effort. To ensure no data loss in this electronic environment, it is essential that key hardware must be resilient and fault tolerant, and the backup and recovery processes must be robust and validated. Backup strategies also need to be developed to ensure that data are not lost if a backup fails. Consider differential rather than incremental backups or full backups that are executed each working day.

The key message when designing electronic workflows is to ensure that once data are acquired at the point of origin they are not printed out or transcribed again but are transferred electronically between systems using validated routines. Paper is not to be used as the transfer mechanism. Rather, the information should only be printed when required (e.g., audits, inspections etc.). Data storage must be networked and robust. Where necessary, thought must be given to file naming conventions to uniquely identify data. And the data should be saved under projects or studies as appropriate.

Organize Your Data for Submission or Annual Reviews

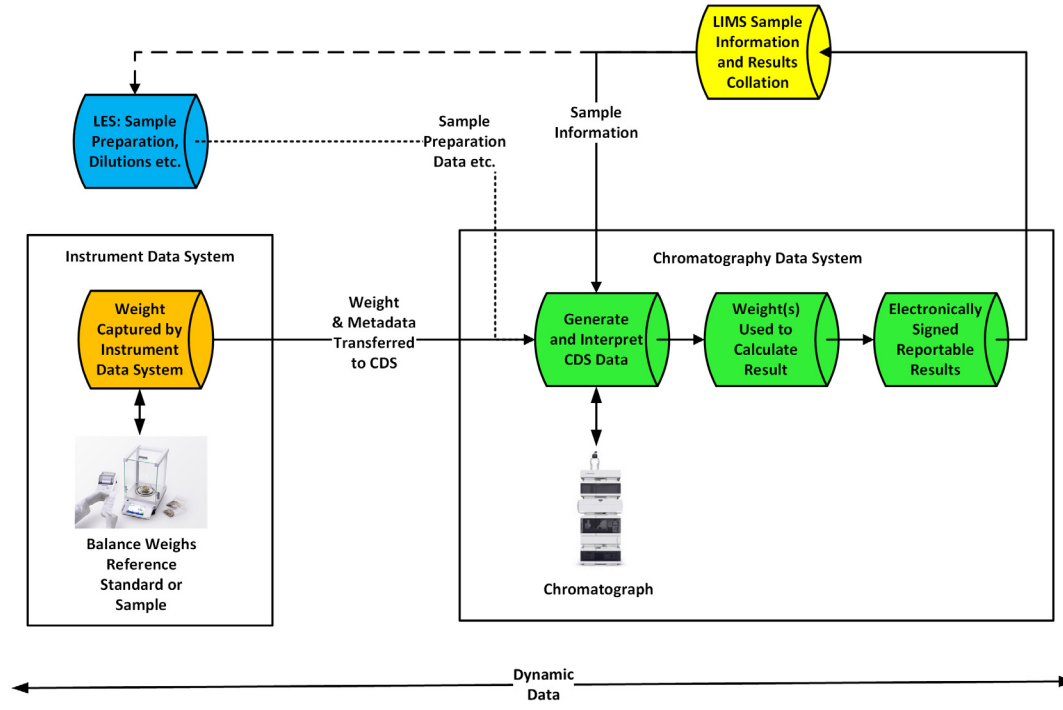
Don't just focus on data storage for product release, but consider what you need to do for either product submissions (Analytical Development) or Annual Product Review/ Product Quality Review (Quality Control). You'll need your data organized so it can be easily retrieved, searched and, where appropriate, abstracted for further data analysis. If organized and structured well, any later search routines as inputs to ML/AI programs will benefit.

Proprietary versus FAIR Data

Most analytical data is in proprietary data formats that tie a laboratory to a specific system and supplier. There have been some previous attempts at standardization of spectroscopic and chromatography data in the late 1980s and 1990s, but these failed because they did not address the contextual metadata, but only the data file. Currently, there are two standardization approaches for laboratory data: AnIML (Analytical Information Markup Language, which is XML based) and Allotrope Foundation (developing binary data formats). These are mutually exclusive standards.

Both standards try to conform to FAIR data principles: Findable, Accessible, Interoperable, Reusable. Standards are very important, as the data from analytical instruments and computerized systems have a longer life than the instruments and systems that generate them. However, current data and metadata must be

FIGURE 2: One way to eliminate Static Data.



converted rather than acquired in a particular data format. Looking outside of the pharmaceutical industry, all long-term digital archiving projects use XML as the foundation.

IDENTIFYING AND ELIMINATING STATIC DATA

In the first eBook, we discussed that static data such as a weight on a balance printout could become dynamic data when entered into a computerized system such as a CDS, ELN or LIMS. This process is inefficient and error prone. It also breaks the second principle of digitalization: never retype data. To eliminate static data, the data along with associated metadata must be captured at the source.

One approach to keeping current with existing technology is shown in FIGURE 2. The informatics applications used are the:

- Laboratory Information Management System (LIMS), shown in yellow, for managing sample information and collating test results.
- Instrument Data System, in orange, interfaced with an analytical balance (interfacing other instrument types is also possible).
- Chromatography Data System, in green.
- Laboratory Execution System (LES), in blue, which is an option for documenting sample preparation and transferring data to the CDS.

Sample and batch information is transferred to the LIMS and then downloaded to the LES and CDS applications. Sample preparation is automated using the LES, and the information such as dilutions are transferred electronically to the CDS. Previously, the weight from the analytical balance is manually entered into the instrument data system, which is slow and error prone. Now, as demonstrated in **FIGURE 2**, we have an instrument data system with an electronic workflow that acquires the balance sample weight and transfers it to the CDS. Further technical controls ensure that the right type of balance is used, or even a specific instrument is identified by its serial number. There is an audit trail to ensure that samples are not weighed into compliance.

The CDS now has all data required. The sequence is run, the chromatographic data files are interpreted and a reportable result is generated. Second person review is accomplished electronically in the various informatics systems. The scope of review is limited by effective use of validated technical controls within the applications:

- No user has deletion privileges, so a reviewer does not need to look for deleted data.
- Data can only be stored in a single location. Therefore, no searches need to be conducted for orphan data in the rest of the system.
- Audit trails in the application highlight modified data, allowing a reviewer to review by exception [7].

The informatics applications ensure that all data are complete, consistent and accurate. This approach also leverages existing technologies, as advocated by the WHO data integrity guidance discussed earlier [8] and expectations of the current cGMP [9,10].

If required, the values from many result sets can be monitored for trends, as required by EU GMP Chapter 6.9 [11], or used to identify errors. This work would not be possible with static data without extensive manual data entry into a spreadsheet.

REDESIGNING PROCESSES: TURNING PRINCIPLES INTO PRACTICE

The way to start redesigning a laboratory process is at Level 1 of the agreed *As Is* process map. The current way of working should be challenged with improvement ideas from laboratory staff, using existing systems better or using a new computerized system. Once the new Level 1 process is agreed upon, the same approach can be undertaken with all Level 2 *As Is* activities.

Redesign of a process is intended to:

- Eliminate unnecessary activities
- Modify processes and activities to be simpler and more efficient
- Introduce new activities that are simpler and easier to perform
- Leverage existing computerized systems by implementing unused functions or by using a new application with better features to obtain business benefit

Case Study Example: Sample Management Process Redesign

You will recall the *As Is* sample receipt and management process shown in FIGURE 3 and discussed in Where Are You Now? Understanding Your Current Processes was the starting point for process redesign. The aim of the process redesign (FIGURE 4) was to come up with a single, simplified and unified process applicable to all samples from whatever source. Several improvement ideas were used to challenge the *As Is* process, to move from three to a single process applicable to all samples.

FIGURE 3: An *As Is* Process Map of Sample Receipt and Management.

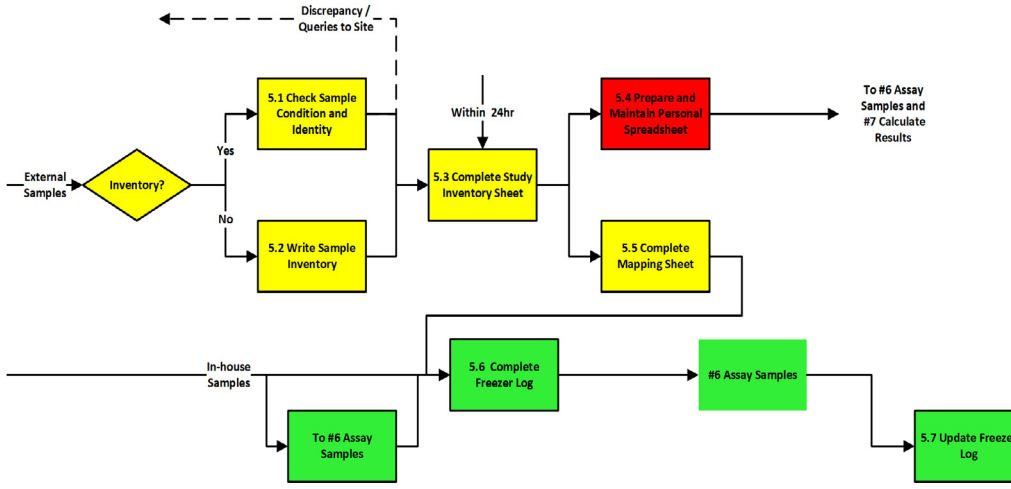
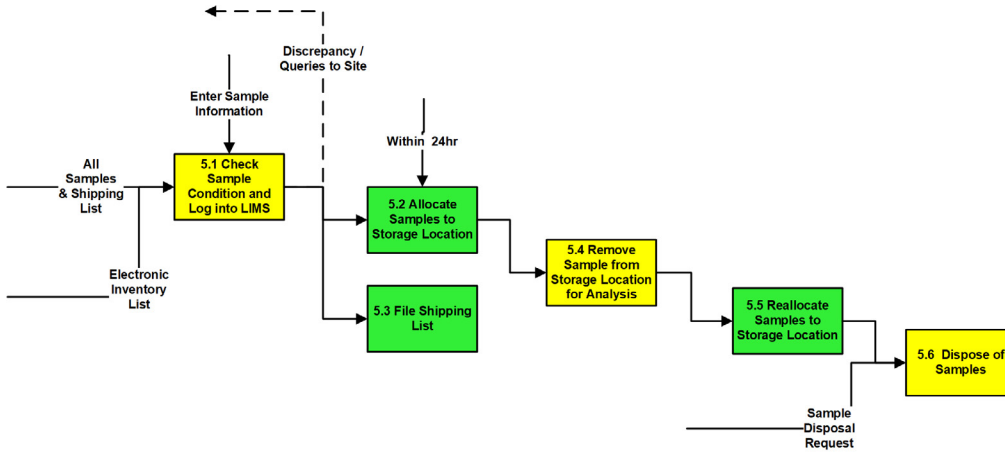


FIGURE 4: The redesigned and simplified Sample Receipt and Management Process



Not only were sample containers barcoded, but there were sample storage locations and shelves within each one. This eliminated the paper logbook used in the *As Is* process. Groups sending samples for analysis were instructed to send an electronic inventory of samples to the laboratory rather than the laboratory having to write one as in the *As Is* process. The only item of paper remaining in the process is the suppling agent's packing list, which is filed after sample receipt is complete.

Case Study Example: Chromatography Process Redesign

Similarly, the three-hybrid system chromatography process shown in FIGURE 5 was redesigned to incorporate all sample calculations performed by the spreadsheet into the CDS and to use electronic signatures. No paper was printed. This approach simplifies the work that needs to be performed by the second person reviewer of the analytical records: fewer transcription error checks and a faster review process. If the CDS highlights data that are changed, this will speed the review process even more. Remember the warning at the start of this article? Users need to see a benefit of using computerized systems. There are benefits to both the analyst and reviewer by eliminating the printing of chromatograms and typing peak areas, weights and factors into a spreadsheet.

FIGURE 5: Chromatographic analysis and hybrid records.

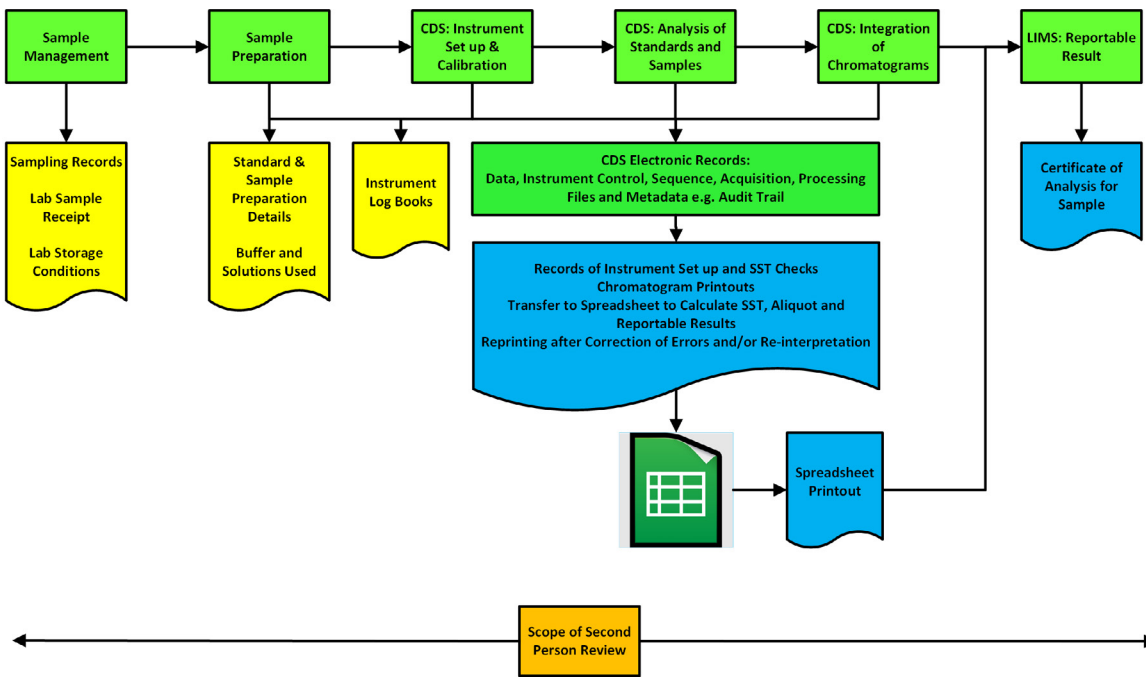
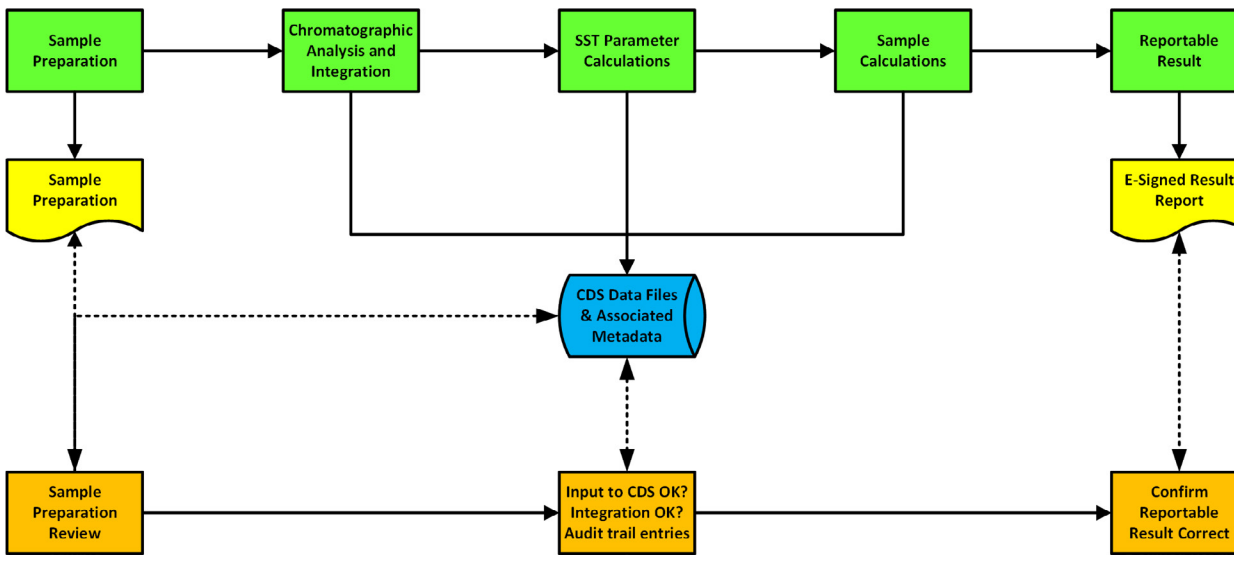


FIGURE 6: Redesigned Chromatography process with elimination of spreadsheet calculations with minimal paper printouts.



However, as you can see on the left of FIGURE 6, paper is still used for documenting the sample preparation process. A CDS cannot automate this, and in a second phase of work the elimination of paper records from sample preparation would be undertaken using either an ELN or LES. So with the proposed *To Be* process, there are business benefits. However, the analyst still must manually input sample information, weights factors, etc. into the CDS and the reviewer must check them. When sample preparation is automated, there is much less work to document manually.

QUICK WINS AND IMPROVEMENT PROJECTS

At the end of the process redesign there will be the To Be process maps plus several Quick Wins and Improvement Projects that will deliver the digitalized laboratory.

- **Quick Wins**
  These are small items of work that are simple and inexpensive to implement, can be done quickly (as the name suggests) but provide business benefit. They are used to provide credibility to the overall digitalization strategy.
- **Improvement Projects**
  These are typically larger and longer time scale projects that require management approval and can take several months.

Case Study: Examples of Quick Wins

In the article Where Are You Now? Understanding Your Current Processes, in the section on Can Systems Perform Better?

an FT-IR spectrometer and an automated dissolution system were presented.

- **Automated Dissolution System**
  Of 49 analytical procedures that use this system, only one uses the system in its fully automated intended use: a tablet or capsule is dropped in each vessel and calculated results come out of the data system at the end of the procedure. The remaining 48 procedures use the system as separate items of instrumentation: dissolution bath, UV spectrophotometer and a spreadsheet. The quick win is to ensure that the 48 methods use the system in fully automatic mode, including use of electronic signatures. This would eliminate the spreadsheet, transcription error checking and speed both the analysis and the review.
- **FT-IR Spectrometer Identity Testing**
  One of the laboratories mentioned only calibrates the FT-IR spectrometer annually with a polystyrene reference standard. However, there are built-in tests that can check the instrument before analysis each day, if required, plus the implementation of the compare function. This will take a little longer than the dissolution system, as there needs to be a short validation to verify that the compare function works. However, the laboratory has a spectral library that is not involved for verification and is simply a check that the sample spectrum matches the reference.

The Portfolio of Improvement Projects

Arising from the process redesign will be several improvement projects that will form a portfolio. One such project could be the modification of the CDS analysis process shown in FIGURE 6. Other improvement projects could be:

- Automation of wet chemistry
- Implementation of a LIMS for sample management, test and result management and reporting
- Elimination of hybrid systems (e.g., thermal analysis, spectroscopic techniques)

Define and Scope Each Project

Each project needs to be defined and scoped accurately:

- Title
- Scope and boundaries (what is in and what is out)
- List problems with the *As Is* situation
- List what will change with the *To Be* situation
- Impact of the change
- Benefits of the project
- Technical feasibility

Costs for the project portfolio are discussed in the next article, Planning the Digitalization Strategy, but prioritization will be discussed in eBook 3.

DOES THE APPLICATION FIT THE LABORATORY OR THE LABORATORY FIT THE APPLICATION?

An interesting philosophical question is, does the application fit the lab or the lab fit

the application? Remember you will have redesigned your processes and when you see an application it may not match it. What do you do now? Don't panic is the best advice. A supplier may have implemented their software after visiting several laboratories and may have developed a generic workflow that can be configured.

We need to be extremely careful about the terms configured and customized.

GAMP 5 Second Edition Appendix M4 [12] defines software categories, and the three that are important in this discussion are:

Software Category 3

- Commercially available non-configurable produc.t
- The business process automated by the software cannot be changed
- The software can be configured to run (e.g., user roles and access privileges, report templates, etc.). However, the business process cannot be changed.
- Some people think that setting a scan range on a UV spectrophotometer is configuration. No, it is parameterization, as the business process is not changed: the spectrometer scans regardless of the scan range input by a user.

Software Category 4

- Commercially available configurable product.
- Software can be changed to match and automate a business process. This can be achieved in a number of ways, such as turning a function on or off, graphically by dragging icons to form a business process or by using a language provided by the supplier of the product. This last option is on the border between Category 4 and Category 5 and must be handled more as custom software.

Software Category 5

- Custom or bespoke application or module.
- Software that is written for a specific purpose and is unique. This is the highest risk software and needs more development than if you were purchasing from a supplier.
- Avoid custom software unless there is a **VERY** compelling business case to do so. A statement that, "We are X," and, "This is the way that we work," only polishes the company ego and leaves an exceptionally large hole in the company bank balance. This is also a legacy nightmare. Don't, just don't.

The first option is that 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 efficient, as we have seen previously where processes have evolved over time, especially if you've had a compliance kicking from an inspector. If this approach is taken, it might result in extensive configuration or even worse, software customization. This is going to be both 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 travelled.

Changing your lab processes is the best option. Although you have a redesigned process on paper, it can still be improved when compared with an application you have not considered before. If possible, keeping the process as close to standard product functionality is the best option for faster implementation and lower validation costs, provided your business objectives are met. Ensure that any configuration ensures protection of electronic records and eliminate data integrity vulnerabilities. Supplier testing can also be leveraged to reduce your validation time and costs, as we shall discuss in eBook 3.

"Although you have a redesigned process on paper, it can still be improved when compared with an application you have not considered before."

THE MISSING PIECE OF THE JIG-SAW

We have focused our discussion on the laboratory to this point. However, there is a hidden component that is a vital foundation to a digitalised laboratory and that is the IT infrastructure and services from an IT function. It is not the aim to discuss in-house or outsourced IT, or to consider if on-premises is better than IaaS or SaaS or vice versa.

Regardless of how it is delivered, a robust, resilient and cybersecure IT infrastructure is an absolute necessity. Once digitalized you can't go back to paper, not even in an emergency. Therefore, the network needs enough capacity to transport your files from source to storage. This may seem trivial if you have worked with a networked CDS for several years, for which data file sizes are between 50 KB and 200 KB for conventional chromatography. If you start to move many diode assay spectra between 1-5 MB, IT may think it's OK but will monitor the situation. However, if you start shifting high resolution spectral data in the order of several GB, there is potential for a bandwidth problem. Similarly, IT needs to consider the impact of the various digitalization projects on storage, backup and failover planning.

The point of this discussion is to ensure that IT are involved in the digitalization project and are aware of the impact of the various projects on the infrastructure so they can plan along with the laboratory.

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Planning the Digitalization Strategy

This article serves as a link to eBook 3, with a brief look at topics that are vital for ensuring the success of a laboratory's digitalization program.

MANAGEMENT SUPPORT

This is the critical success factor in the digitalization of a laboratory. As noted earlier, this is a journey and not an event. You will need senior management approval initially and throughout the program. Support comes in different forms:

- Acknowledgement that the laboratory needs to improve
- Supporting the process mapping and redesign work and providing facilities and resources to allow it to take place
- Review of the quick wins and implementation projects and associated budgets, including cost estimates and resource requirements both internally and externally
- Communication between the laboratory and departments supplying samples and using the analytical data

The major support comes when the Quick Win and implementation projects start:

- Visible and public support of all projects, including supporting each one with finance and resources
- Communication between senior management, project team members, laboratory staff, QA and IT

If Gemba walks are used by senior management to see how an organization is functioning, such as part of a data integrity program, a similar approach can be used to have discussions about the digitalization projects.

COST ESTIMATES FOR UPGRADES, RESOURCES AND PROFESSIONAL SERVICES

Each of the improvement projects identified out of the process mapping and redesign need to be budgeted in the following areas, as applicable:

- Application software
- Hardware including physical IT hardware (if virtual infrastructure is not used), analytical instruments with any accessories and laboratory hardware such as data servers.
- Qualification documentation, including any execution costs. Please review before purchase to ensure that the quality is adequate.
- Training requirements (this area is usually overlooked or a train the trainer approach is adopted). Depending on the nature and size of a project, determination should be made on a case-by-case basis (e.g., an instrument may just require use and maintenance compared with a networked computerized system that may require user, supervisor and administrator training).
- Professional services from the supplier, contractor or consultant to help with set-up of the system, interfacing, configuration or validation.
- Internal resources must be included in the budget. This is an area that is overlooked frequently. Expecting a key resource to continue their daily responsibilities and not working side by side with the project team can seriously impact the desired outcome. There might be the need to backfill positions with temporary staff for larger projects.

One outcome of the process redesign is a consideration of harmonization of instrumentation from a specific supplier with the use of their instrument data system software. Equally so, standardization of a specific application software across an organization would reduce costs of qualification and validation. In cases such as these, it is important to win hearts and minds of all organizational departments involved rather than by management diktat.

When generating the budget for each project, it is important to include contingency both in time to complete each

project but also finance. For the latter, it depends on an organization's approach to contingency, if the money has to be hidden in other items or be a line item. But based on personal experience, a contingency fund is often essential.

GENERATING THE DIGITALIZATION BUDGET

As digitalization is a journey, all projects will not be completed within a single financial year. Projects will run over several years, as will the budget. Justification for each project must be sound and demonstrate a return on investment. Reliance on compliance with GMP regulations is not going to win approval from the Chief Financial Officer. Return on cash will.

The complete digitalization program must have sound scientific and business driven justification. Many of these digitalization projects will require approval of the Corporate Board members. One such project that I was involved in was a multi-million Euro project to automate seven QC laboratories around the globe. Funding for the project required approval by the Board.

NEXT EBOOK

In the last eBook of this trilogy, we will look in more detail at implementing Quick Wins and running Improvement Projects, including managing project (not regulatory) risk. This includes how to best define user requirements and cost-effective computerized system validation, whether for a completely new system or an upgrade of an existing one.

We will look in more detail about the role of management in these projects, not forgetting the role of users to make or break a strategy.

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Bob McDowall is an analytical chemist with 50 years of experience, including 15 years working in the pharmaceutical industry, followed by 29 years working for the industry as a consultant. He has over 35 years' experience in automating laboratories and computerized systems, mainly involving analytical systems and laboratory informatics. Bob edited the first book on Laboratory Information Management Systems (LIMS) in 1987 and he is the 1997 LIMS Awardee from the LIMS Institute presented for advances and training in the subject.

He was a co-author of the revision of USP <1058> on Analytical Instrument Qualification that integrated instrument qualification and computerized system validation that was updated in 2017. Bob has also been involved with the validation of computerized systems for over 30 years and is the author of Validation of Chromatography Data Systems, 2nd Edition published in 2017. His latest book is Data Integrity and Data Governance: Practical Implementation for Regulated Laboratories was published in 2019 by the Royal Society of Chemistry.

He is a member of the GAMP Data Integrity Special Interest Group, contributing to the Records and Data Integrity Guide in 2017 and two Good Practice Guides on Data Integrity Key Concepts and Data Integrity by Design. Bob is a lso the author of the "Questions of Quality" and "Focus on Quality" columns in LCGC Europe and Spectroscopy magazines, respectively.