LCGC®

JULY 2022

# Pharma 4.0 and the Digital Regulated Laboratory

## Part 1: Why Digitalize Your Regulated Laboratory?

- What is Pharma 4.0?
- Data Integrity Within a Pharmaceutical Quality System
- A Flexible Analytical Data Life Cycle
- Business Drivers for Digitalization

This custom ebook is sponsored by Agilent Technologies, Inc. and presented in partnership with *LCGC*.

Agilent

# Introduction

***This is the first in a series of three eBooks discussing and offering practical advice on the journey from your current ways of working to a digital laboratory operating in a regulated environment.***

In 1993, shortly after the Barr Laboratories court case [1-3], the FDA published a document entitled Inspection of Pharmaceutical Quality Control Laboratories [4]. The first half of the document can be ignored as it covers Out of Specification (OOS) results which has been replaced by the 2006 and 2022 FDA Guidances on Investigation of Out of Specification Results [5.6]. However, sections 13 – 21 are still valid as many regulated laboratories have changed little in 30 years.

This is mainly due to a lack of investment which means that many small and medium sized regulated laboratories have failed to keep current with advances in science and technology. This can be due to management complacency believing that if we passed the last inspection, we would pass the next one. As we will see with some FDA warning letters, failure to connect laboratory instruments to an informatics application or even purchasing an instrument that can store electronic records but failing to do so and rely on printing paper can result in warning letter citations.

Keeping current is a regulatory requirement in both Europe and the USA, but many companies fail to understand the meaning of the “c” in cGMP or ignore it altogether. We will discuss this point in more detail later in this eBook.

Data integrity is also a driver for change: the WHO Good Records and Data Management Guideline from 2016 [7] and PIC/S PI-041 Data Integrity guidance document [8] both state that “hybrid systems are not encouraged and that hybrid systems should be replaced at the earliest opportunity.” In many laboratories, paper records are paramount and spreadsheets (both validated and unvalidated) are used extensively instead of incorporating calculations into informatics applications to avoid printing and manual entry into a spreadsheet. We need to understand the importance of Analytical Instrument Qualification (AIQ) and Computerised System Validation (CSV) in meeting regulatory requirements and ensuring data integrity.

# Introduction

However, the primary goals of AIQ and CSV are to determine if you have purchased the right instrument or system, and have you generated business benefit?

Digitalization has one potential flaw: are supplier applications fit for purpose in a digitalized and regulated laboratory? When you look outside of the mainstream networked laboratory applications such as LIMS, CDS, ELN and LES, many other applications lack basic compliance and data integrity technical controls. You can't aim for Pharma 4.0 with Supplier 2.0 [M.Newton, Personal communication]. As PIC/S PI-041 notes, "Specific attention should be paid to the purchase of GMP/GDP critical equipment to ensure that systems are appropriately evaluated for data integrity controls prior to purchase [8]." It is imperative that sufficient due diligence is conducted to assess technical controls before purchasing an application or an instrument with controlling software.

Underpinning all of this is one critical requirement: a robust and resilient IT infrastructure. It is not the role of this series to discuss if the best IT infrastructure is on premises or in the cloud. BUT, it is imperative that any IT infrastructure has sufficient computing power, network speed and bandwidth, data storage, cybersecurity and resilience. If an organisation's records are all electronic and the network is down, or malware has encrypted all data then major disruption occurs.

These three eBooks are intended to be a guide for a regulated laboratory journey from where it is now on a journey to a digital laboratory. GMP regulations require interpretation. While all laboratories analyze samples, the way that an individual laboratory operates differs due to points such as:

- Interpretation of the regulations: from light touch to stringent
- Compliance history with regulatory authorities
- Under-investment in instruments and computerized systems by the company: some laboratories may resemble an analytical instrument museum

## Understanding Digitization and Digitalization

It is important that we define and understand the two terms from the beginning of this series.

- **Digitization:** *converting from paper to digital format*.

  The easiest way to understand this is the conversion of paper SOPs to electronic format by scanning a signed paper procedure then issuing the scanned electronic copy for use. Periodic review of each procedure would be triggered manually, and replacement of obsolete SOPs must also be performed manually. In essence, it is the automation of the status quo with all the inefficiencies of the paper process.

# Introduction

- **Digitalization:** *the application of informatics applications to transform the ways of working.*

  Taking the SOP example above, digitalization would use a document management solution to manage the writing and reviewing with authorization by electronic signatures and then publishing online. Periodic reviews of each procedure would be triggered automatically by the system. After updates have been issued, obsolete copies are archived automatically. Paper has been eliminated from the process, which is faster and more efficient.

This series will focus on digitalization of a regulated laboratory.

## Overview of the Three eBooks

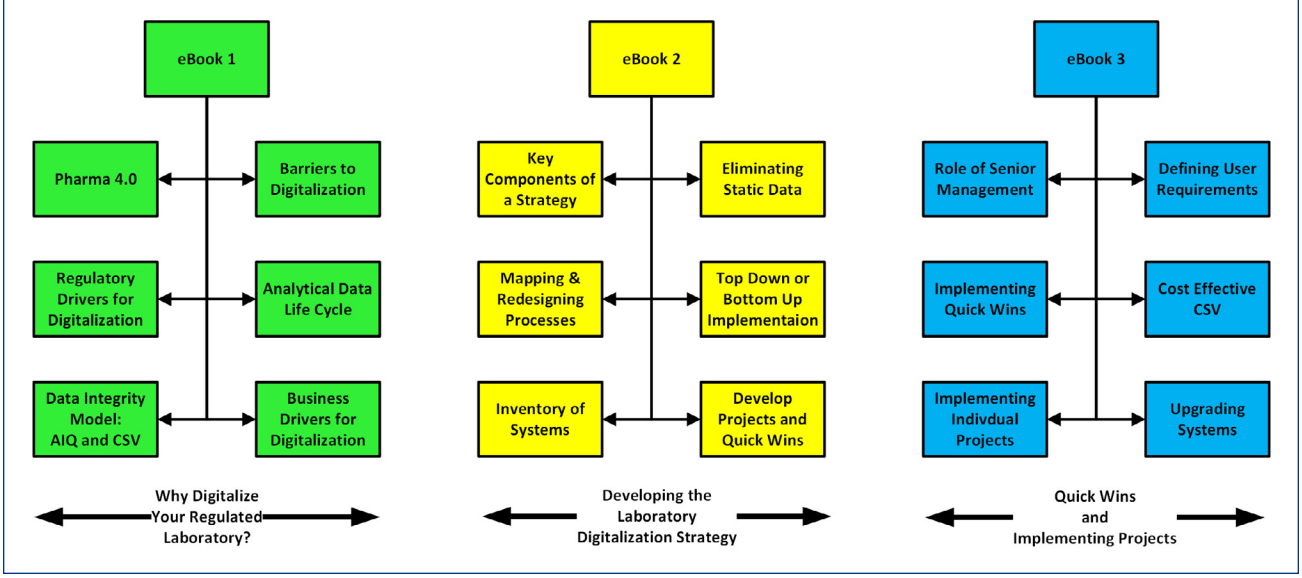
As mentioned above, this is the first in a series of three eBooks on planning and realizing a digital regulated laboratory (FIGURE 1). The series is aimed mainly at Good Manufacturing Practice (GMP), but the principles outlined here can also be used for laboratories working to Good Laboratory Practice (GLP).

The three e-Books look at the journey from where you are now, assessing systems and processes, planning how to automate your laboratory in stages, and finally, implementing quick wins and projects.

### eBook 1: Why Digitalize Your Regulated Laboratory?

We start from what is happening in the wider world with Industry 4.0 and Pharma 4.0 and then move on to looking at the regulatory drivers for digitalization while keeping current

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



with GMP, understanding the cost of compliance versus the cost of noncompliance, and learning from the mistakes of others with citations in some warning letters.

The importance of analytical Instrument qualification (AIQ) and computerized system validation (CSV) in ensuring data integrity is shown via a Data Integrity Model. We then look at some of the barriers to digitalization: spreadsheets, hybrid systems and static data. Even when there is the capability for better working, many laboratories use a chromatography data system (CDS) as an electronic ruler and resort to using spreadsheets to calculate system suitability test (SST) and reportable results. Consideration of data integrity in any laboratory's digitalization program is critical. Are you perpetuating the data integrity problem by purchasing computerized systems with inadequate technical controls to ensure the integrity of records?

A flexible analytical data life cycle is discussed, because there is no one-size-fits-all life cycle for analytical procedures and the data generated by them. Some critical procedures develop static data, which needs to be addressed in the automation strategy for the laboratory.
As a lead into the next eBook, we will discuss the business drivers for digitalization and why we need to have an overall laboratory automation strategy.

**eBook 2: Developing the Laboratory Digitalization Strategy**
Where are you now, and where do you want to be? The three rules of laboratory automation will begin the second eBook discussion for digitalization of a laboratory, along with its application to process understanding and redesign for more efficient and effective electronic working. An inventory of current systems and their capabilities to automate the new ways of working must be generated. It is likely that some systems will not be capable of automating the new ways of working and need to be replaced. This requires the availability of both human and financial resources, and hence, the role of senior management is key supporting the approach. To enable a big picture visualization of the approach, a laboratory automation strategy is essential with timescales and resources (with contingency) that outline projects to achieve the digitalization process for a laboratory.

The other areas in any automation strategy are the business processes, which need to be digitalized. How efficient are they? Are there any data integrity vulnerabilities that need to be resolved?

**eBook 3: Quick Wins and Implementing Projects**
A strategy is fine but it has to be delivered, ideally on time and on budget. There are two main ways to achieve this with the portfolio of projects in the strategy: top down or bottom up. Which is the best? However, there are quick wins to implement first. These are improvement ideas that can be implemented quickly and with relatively little cost. These give the strategy credibility, and more so when senior management is encouraging the staff to work smarter and use these new systems.

# Introduction

The first major project is critical to the success of the laboratory and credibility of the strategy. This requires project risk to be minimized to ensure success, but also regulatory and implementation risk. Simpler and easier projects with no custom software development is essential 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 and manage risk and apply sound science to focus scarce resources to where they are most needed.

As the strategy progresses, new technologies come along. This may require a revision of the overall strategy. This is normal and should be expected.

The aim of these three eBooks is to provide you with a comprehensive roadmap to allow any regulated laboratory to transition from processes involving paper records to with hybrid computerized systems to fully electronic processes with electronic signatures.

## References


1. *Barr Laboratories: Court decision strengthens FDA's regulatory power.* 1993; Available from: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm212214.htm.
2. C.L.Burgess, *Issues related to United States versus Barr Laboratories inc., in Development and Validation of Analytical Methods*, C.L.Riley and T.W.Rosanske, Editors. 1996, Pergammon Press: Oxford. p. 352.
3. R.J.Davis, *Judge Wolin's interpretation of curent Good Manufacting Practice Issues contained in the Court's ruling United States versus Barr Laboratories, in Development and Validation of Analytical Methods*, C.L.Riley and T.W.Rosanske, Editors. 1996, Pergammon Press: Oxford. p. 252.
4. *Inspection of Pharmaceutical Qualiy Control Laboratories.* 1993, Food and Drug Administration: Rockville, MD.
5. *FDA Guidance for Industry Out of Specification Results.* 2006, Food and Drug Administration: Rockville, MD.
6. *FDA Guidance for Industry Out of Specification Results.* 2022, Food and Drug Administration: Rockville, MD.
7. *WHO Technical Report Series No.996 Annex 5 Guidance on Good Data and Records Management Practices*. 2016, World Health Organisation: Geneva.
8. *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.



**R D McDowall, PhD**

Director

R D McDowall Limited


# What is Pharma 4.0?

Industry 4.0, or the 4th Industrial Revolution, refers to the use of components such as smart automation, Internet of Things (IoT), robotics, machine learning and artificial intelligence, connectivity between computerized systems and cloud computing to improve the way that industry automates processes.

Pharma 4.0 is a sub-set of Industry 4.0 that is obviously focused on the pharmaceutical and biotechnology industries and the contract organizations that support them. The problem is that there is a broad spectrum of regulated laboratories within these entities. Some are automation light, with islands of automation in an ocean of paper, and others are well on the way to being digitalized.

## IS AN AUTOMATED LABORATORY PAPERLESS, ELECTRONIC OR DIGITALIZED?

Yes! This is the simple answer. All three terms can apply to an automated laboratory. In the beginning, the aim was for a paperless

laboratory but with no regulation for the use of electronic signatures. The problem was how to author and review the records. With the publication of 21 CFR 11 final rule in 1997, there was the ability to author and approve records with electronic signatures [1].

It requires laboratory informatics applications to incorporate the technical controls in the software to comply with the regulation to enable a laboratory to become automated or digitalized.

Let us start the journey by asking some pointed and often uncomfortable questions.

## HOW GOOD IS YOUR LABORATORY?

Let me ask you some leading questions:

- Are you analyzing samples in a timely manner?
- Are you still printing paper reports?
- How do ensure data integrity with manual processes and records from hybrid systems?
- Are you using your CDS as a typewriter as all post run calculations are performed by spreadsheets?
- Do you selectively report results? When a batch fails, just repeat an analysis until you get the "right" result?
- Are your deviations investigated scientifically?
- Does second-person review take longer than the actual analysis?
- When was the last time you reviewed your lab processes and decided to improve your workflows?
- Does it take you a long time to prepare for inspections?

These are questions you should ask yourself as you prepare a digitalization strategy to move away from manual and hybrid processes that lead to transcription errors, reduce lab productivity and impact data integrity. However, one of the roadblocks in your way is senior management.

## CONVINCING SENIOR MANAGEMENT TO INVEST

Many laboratories complain that they cannot automate due to no time available or no money. Both problems are the responsibility of senior management. It is surprising that in organizations that complain there is no money available to invest in automation a treasure chest of cash can be found after a mauling from a regulatory inspection. Therefore, before getting into digitalization we need to give senior management an understanding of the current regulatory environment via regulatory citations and the balance between the cost of compliance and the cost of noncompliance. All of which come down to understanding what current means in current Good Manufacturing Practice.

## REGULATORY DRIVERS FOR LABORATORY DIGITALIZATION

### Understanding Regulations: Understanding What Current GMP Means Is Important

Most analytical scientists working in a Quality Control or Analytical Development

laboratory will refer to GMP regulations, however the formal title of 21 CFR 211 is Current Good Manufacturing Practice for Finished Pharmaceutical Products or cGMP regulations [2].

- Is current important?
- What does current mean?

To answer these questions, we must go back to September 29, **1978** where the preamble to FDA regulation 21 CFR 211 on Current Good Manufacturing Practice for Finished Pharmaceutical Goods was published [3]. Preamble comment 17 has the following statements that have been edited for brevity:

> *Several comments objected to the word "current" in the title and text of the regulations….*
>
> *Several of these comments reflect, the Commissioner believes, a misunderstanding regarding the use of the word "current"….*
>
> *Although the practices must be "current" in the industry, they need not be widely prevalent.*
>
> *Congress did not require that a majority or any other percentage of manufacturers already be following the proposed mandated practices, as long as it was* ***a current good manufacturing practice*** *in the industry e.g.* ***it has been shown to be both feasible and valuable in assuring drug quality [3].***

The takeaway message from this is that laboratories must keep current with technologies and implement new approaches and systems to keep "current". This is also mirrored in a page on the FDA website that says:

> *Accordingly, the "C" in CGMP stands for "current,"* ***requiring companies to use technologies and systems that are up-to-date in order to comply with the regulations. Systems and equipment*** *that may have been* ***"top-of-the-line"*** *to prevent contamination, mix-ups, and errors* ***10 or 20 years ago may be less than adequate by today's standards [4].***

Is this approach to keeping current unique and only applicable to the FDA?

No, it is mirrored in Article 23, §1 of European Directive 2001/83/EC that requires a marketing authorization holder to:

> *After a marketing authorization has been granted, the marketing authorization holder shall, in respect of the methods of manufacture and control provided for in Article 8(3)(d) and (h),* ***take account of scientific and technical progress*** *and* ***introduce any changes*** *that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods [5].*

Therefore, both FDA and European Union regulations expect laboratories to keep up with technologies and be subject to

continual improvement, as required by ICH 10 on Pharmaceutical Quality Systems [6] and EU GMP Chapter 1 [7].

However, the situation in many laboratories does not match the requirements either to keep current or take account of scientific and technical progress. In general, a lazy approach is prevalent: if it was good enough last inspection, it will be good enough for the next one.

The one regulatory guidance document that advocates process efficiency is the WHO Good Record and Data Management Practices guidance from 2016 [8] which states in section 5.6:

> *A data management program developed and implemented on 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.*

It is unusual to find a regulatory guidance document recommending business process efficiencies and effectiveness. However, there are two points to be made here:

1. Use laboratory informatics solutions to streamline processes
2. Eliminate paper and have only a single medium to review and retain

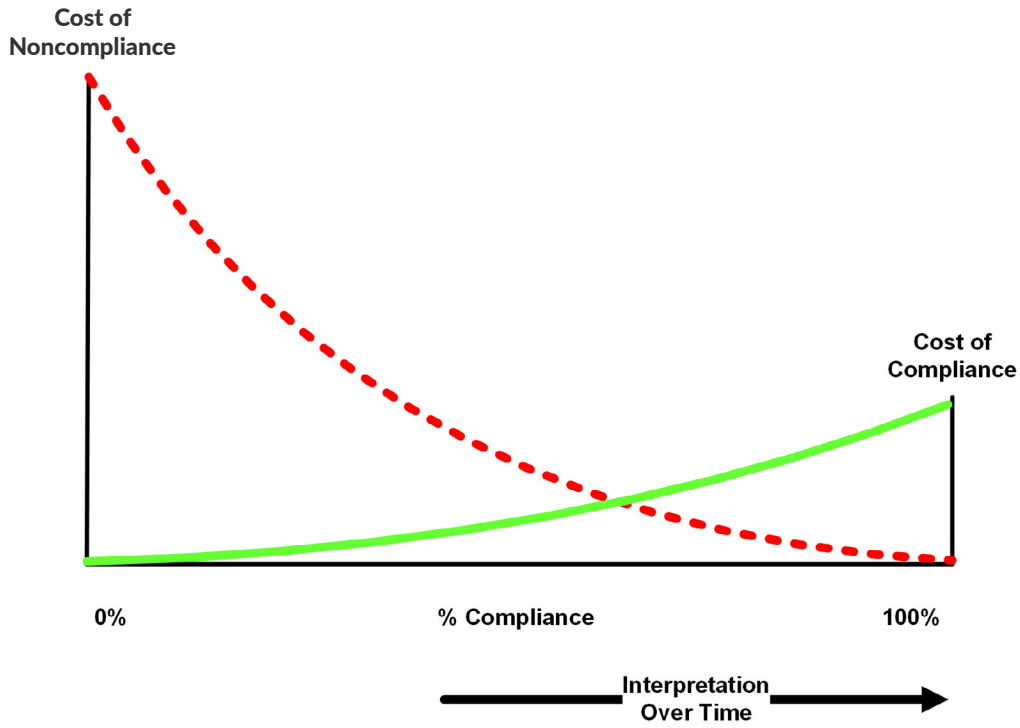
This is coupled with statements that hybrid systems are not encouraged and hybrid systems should be replaced at the earliest opportunity [8]. We will return to this WHO section and discuss it in more depth later in this e-Book.

Given that there is a regulatory expectation that industry must keep current and that, in general, industry totally ignores this, we need to discuss the consequences of failing to keep current. Please show the next section to your Senior Management.

## COST OF COMPLIANCE V COST OF NONCOMPLIANCE

Risk management is one of the requirements for the pharmaceutical industry following the publication of the FDA's GMPs for the 21st Century [9] and ICH Q9 on Quality Risk Management [10]. How much work is required in a regulated laboratory is dependent on a justified and documented risk assessment that must also be scientifically sound according to 21 CFR 211.160(b) [2]. This discussion can be summarized as the balance between the cost of noncompliance versus the cost of compliance. Each laboratory makes the decision along a spectrum from doing nothing to doing everything that is possible, and this determines how much regulatory and business risk a company wishes to mitigate or carry as well as how much money the company wishes or must spend.

**FIGURE 1:** Understanding the balance between the costs of compliance and noncompliance [4].




The left-hand vertical axis of FIGURE 1 [4] is the cost of noncompliance, and the right-hand axis demonstrates the cost of compliance. You will note that the cost of noncompliance is much larger than the cost of compliance. One viewpoint is that the former axis is logarithmic, and the latter is linear. This is one of the balances you need to consider. The right-hand side shows the cost of doing it right the first time, and the left-hand side is the cost of getting caught. Fixing a regulatory problem that has been identified in a warning letter is always more expensive than doing the right job the first time or finding a problem and fixing it yourself. If any reader is in doubt about the cost of noncompliance for data integrity violations, I suggest you read a consent decree such as that for Ranbaxy [12]. Here, the cost of noncompliance can be quantified as a $500 million fine plus corrective actions and lost commercial opportunities running into hundreds of millions of dollars.

In FIGURE 1 [4], the horizontal axis is the percentage of compliance from 0% to 100%. The only fixed points are at the ends of the scale where 0% is no control of the process or system and 100% is anything that can be compliant is compliant. In between is a relative scale of compliance. The major point to note is that this scale is not fixed

but moves as indicated by the arrow at the bottom of the figure. But the direction of movement is only one way, and that is to the right! To understand this point, consider the situation with data integrity. The FDA GMP regulations have changed little since 1978 and have always contained data integrity requirements. However, since the Able Laboratories fraud case in 2005 [13] and discovery of industrial scale data falsification and poor data management practices, we have seen a tightening of interpretation by regulatory authorities and the issuance of guidance documents [8, 4, 15-17]. Same regulations but more stringent interpretation. The compliance scale has moved to the right.

## LEARNING FROM THE MISTAKES OF OTHERS

One corollary of Murphy's Law is Horner's Five Thumbed Postulate that states, "The amount of experience gained is directly proportional to the number of systems ruined." As a result, gaining the experience to achieve data compliance can be a long and expensive process. A quicker option is to learn from others' mistakes. For a regulated GMP laboratory, a good way to achieve this is to use the citations in FDA warning letters and 483 observations. We will look at three warning letters issued since 2020 to see the issues that can arise that impact digitalization of regulated laboratories. For more detailed discussion of these three warning letters, there are two articles published by the author [18, 19].

The first two FDA warning letters were issued to Stason Pharmaceutical and tender Corporation in July 2020 [20, 21]. Interestingly each organization was cited under a different part of 21 CFR 211:

- Stason Pharmaceutical: Failure to control computerized systems under 211.68(b)
- Tender Corporation: Failure to set laboratory controls under 211.160(b)

Although cited under different sections of the GMP regulations, the extensive remediation mandated by the FDA was almost identical. A few of the key citations are:

- Executive management oversight of computerized systems and data
- Quality oversight of computerized systems by knowledgeable staff
- Little or no understanding of the data integrity risks posed by laboratory processes coupled with lack of technical controls including audit trails turned off
- *Technological improvements to increase the integration of data generated through electronic systems from standalone equipment (e.g., balances, pH meters, water content testing) into the LIMS network [20, 21]*

Here we have a clear example of a regulatory agency mandating interfacing analytical instruments into a LIMS network. This could be via an instrument data system

or directly into a LIMS or similar application. The message is, if a company can't keep current by their own volition, the FDA will ensure that they comply through warning letter citations.

An FDA warning letter was issued to BBC Group in August 2021 for GMP violations [22] that indicates that the FDA now mandates more stringent remediation. Citation 1 has five main areas of regulatory concern:

- Loss of three years of electronic records from a chromatography data system (CDS)
- Shared accounts, with no password and where users have administrator privileges
- The audit trail of the CDS was not enabled
- Focus on paper printouts and electronic records not saved
- Spreadsheets were uncontrolled and unvalidated: data could be manipulated

Apart from the loss of data and the perennial use of invalidated spreadsheets, the most interesting citation from the perspective of digitalization is the focus on paper printouts and electronic records not being saved.

> *…. you did not retain all original, dynamic records, obtained during the course of testing on other laboratory equipment.*
>
> *Your **viscometer and UV-Vis spectrophotometer had the capability to save data** from product/material testing. Despite having this capability, **your analysts failed to save the complete, dynamic testing data,** and therefore the data was not available for review by the FDA investigator [22].*

The viscometer was used to analyze finished drug products and the UV-Vis spectrophotometer was used to measure ethanol content during raw material testing. This indicates the interpretation of current by the FDA. Twenty years ago, the practice of paper printouts from such instruments would be accepted by inspectors. Now, if an instrument can capture and store raw data, it must be enabled and used.
Some viscometers can capture videos of the analysis to provide objective evidence for reviewers and inspectors post analysis. The failure to capture such electronic records now results in a citation. Question 12 of the FDA Data Integrity guidance states that as soon as you start creating a GMP record it must be saved:

> *FDA expects processes to be designed so that data required to be created and maintained cannot be modified without a record of the modification [17].*

If a laboratory won't digitalize on their own, and if the noncompliance is serious enough, then the FDA will make them via warning letters and 483 observations. I refer you to the associated discussion to see that this is not the right way do undertake digitalization. If a laboratory does not digitalize there can be expensive

remediation costs with an aggressive timescale that is determined by the need to convince a regulator that the company is serious about compliance. This is not the best way to digitalize a laboratory.

However, the issues raised in these three warning letters bring us to another driver for digitalization: data integrity. To understand the importance of digitalization and data integrity and how both are underpinned by Analytical Instrument Qualification and Computerized System Validation we need to examine a Data Integrity Model.

**References:**


1. *21 CFR 11 Electronic records; electronic signatures, final rule*, in *Title 21* 1997, Food and Drug Administration: Washington, DC.
2. *21 CFR 211 Current Good Manufacturing Practice for Finished Pharmaceutical Products*. 2008, Food and Drug Administration: Sliver Spring, MD.
3. *21 CFR 211 - Current Good Manufacturing Practice for Finished Pharmaceuticals*. Federal Register, 1978. **43**(190): p. 45014 - 45089.
4. *Facts About the Current Good Manufacturing Practices (CGMPs)*. 2021; Available from: https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps.
5. *Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use*. Official Journal of the European Union, 2001. **311,** (28 Nov 2001): p. 67.
6. *ICH Q10 Pharmaceutical Quality Systems*. 2008, International Conference on Harmonisation: Geneva.
7. *EudraLex - Volume 4 Good Manufacturing Practice (GMP) Guidelines, Chapter 1 Pharmaceutical Quality System*. 2013, European Commission: Brussels.
8. *WHO Technical Report Series No.996 Annex 5 Guidance on Good Data and Records Management Practices*. 2016, World Health Organisation: Geneva.
9. *FDA Pharmaceutical cGMPs for the 21st Century: A Risk-Based Approach*. 2002, Food and Drug Administration: Rockville, MD.
10. *ICH Q9 Quality Risk Management*. 2005, International Conference on Harmonisation: Geneva.
11. R.D.McDowall, *Validation of Chromatography Data Systems: Ensuring Data Integrity, Meeting Business and Regulatory Requirements* Second Edition ed. 2017, Cambridge: Royal Society of Chemistry.
12. *Ranbaxy Laboratories Ltd & Ranbaxy Inc: Consent Decree of Permanent Injunction*. 2012.
13. *Able Laboratories Form 483 Observations*. 2005; Available from: https://www.fda.gov/media/70711/download.
14. *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.
15. *MHRA GMP Data Integrity Definitions and Guidance for Industry 2nd Edition*. 2015, Medicines and Healthcare products Regulatory Agency: London.
16. *MHRA GXP Data Integrity Guidance and Definitions*. 2018, Medicines and Healthcare products Regulatory Agency: London.
17. *FDA Guidance for Industry Data Integrity and Compliance With Drug CGMP Questions and Answers* 2018, Food and Drug Administration: Silver Spring, MD.

18. *R.D.McDowall, Do You Really Understand the Cost of Noncompliance?* Spectroscopy, 2020. 35(11): p. 13-22.
19. R.D.McDowall. *Achieving Data Compliance: What Not To Do.* 2021; Available from: https://www.technologynetworks.com/informatics/how-to-guides/achieving-data-compliance-what-not-to-do-355284.
20. *FDA Warning Letter Stason Pharmaceuticals, Inc.* 2020; Available from: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/stason-pharmaceuticals-inc-604889-07082020.
21. *FDA Warning Letter Tender Corporation* 2020; Available from: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/tender-corporation-599789-07232020.
22. *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.

**R D McDowall, PhD**

Director

R D McDowall Limited

Agilent

Trusted Answers

# Bring More Flow to Your Workflows

## Learn how Agilent SLIMS enables pharmaceutical labs to go digital

Now there is a practical way to drive the digital transformation of your lab. SLIMS merges the best of a LIMS and the best of an ELN into a single digital system that supports your lab's unique processes and requirements.

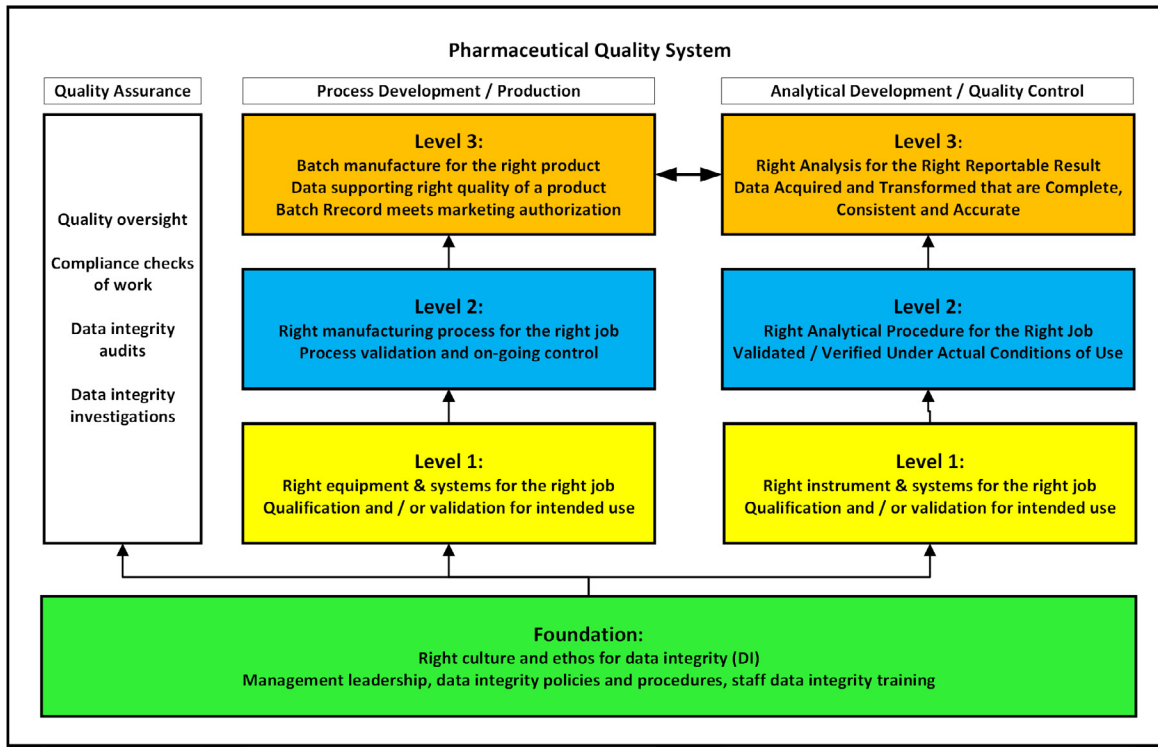
See how SLIMS can minimize the cost and complexity of going paperless. Visit our site for more information, then contact us for a demo.

Learn more about Agilent SLIMS at: SLIMS for Pharmaceutical Labs | Agilent


# Data Integrity Within a Pharmaceutical Quality System

Over the past decade, pharmaceutical regulation has focused on the development of the pharmaceutical quality system (PQS) based on the ISO 9000 quality management system (QMS) following the publication of ICH Q10 [1], and the update of EU GMP Chapter 1 [2]. In a PQS, senior management have overall responsibility and accountability of all activities and data generated [2]. Although data integrity has always been implicit in regulations, section 1.9. of EU GMP Chapter 1 was updated so that work performed by Quality Control laboratories must meet the following:

**FIGURE 1:** A Data Integrity Model [3, 4].






*(iv) Records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting and testing procedures were actually carried out. Any deviations are fully recorded and investigated [2].*

Implicit in this definition is that the records generated have adequate quality and integrity. EU GMP Chapter 4 on documentation and Annex 11 for computerized systems are being revised to emphasize data integrity more than they do currently.

## DATA INTEGRITY MODEL

To understand the scope of data integrity, a four-layer model has been developed covering development, production, quality control (QC) and quality assurance (QA). The full GMP model is discussed in my books [3, 4]. The four layers are shown in FIGURE 1 [3,4] and are described below, for regulated laboratory and QA only:

- **Foundation: Right Corporate Culture for Data Integrity**
  The foundation goes across all elements in an organization and is the Data

Governance layer. The elements here for data integrity are management leadership; data integrity policies, including data ownership; staff training of these procedures; management review, including quality metrics; and the establishment and maintenance of an open culture with ethical work by all staff.

- **Level 1: Right Instrument or System for the Job**
  Analysis requires analytical instruments and a computer application to ensure data quality and data integrity. Instruments must be qualified, and software, including spreadsheets, must be validated. Included here are calibration, point of use checks, or system suitability test samples to confirm that an analytical instrument or laboratory computerized system is within user specifications before use.
- **Level 2: Right Analytical Procedure for the Job**
  For a laboratory, this is validation or verification of analytical procedures under actual conditions of use. What is not covered in current regulations or guidance is method development, which will determine the robustness of the procedure. This is the subject of a USP general chapter <1220> [5] on analytical procedure lifecycle (APL). ICH Q2(R2) and ICH Q14 were issued for public comment on the same subject in March of 2022 [6, 7].
- **Level 3: Right Analysis for the Right Reportable Result**
  Here, process development and production provide the laboratory samples for analysis, which are taken to demonstrate adequate product quality and conformance with the product specification in the Marketing Authorization (MA). It is this level where the work of the three layers are essential for work to be performed ethically and correctly. Where deviations occur, they are investigated.
- **Quality Oversight**
  Although shown on the left of FIGURE 1 [3,4] because of the sample link between production and quality control, the QA function is pervasive throughout the Data Integrity Model to provide quality oversight of both production and laboratory operations (e.g., ensure compliance with regulations plus company policies and procedures) as well as perform data integrity audits and data integrity investigations.

## LEVEL 1: INTEGRATED INSTRUMENT QUALIFICATION AND COMPUTER SYSTEM VALIDATION

There is little point in carrying out an analysis if an analytical instrument is not adequately qualified or the software that controls it or processes data is not validated for the intended uses. Therefore, at Level 1, the analytical instruments and computerized systems used in the laboratory must be qualified for the specified operating range and validated for their intended purpose, respectively. There are the following sources:

- USP <1058> for Analytical Instrument Qualification, 2018 version [8]
- GAMP Good Practice Guide for Validation of Laboratory Computerised Systems, 2nd Edition [9]
- Validation of Chromatography Data Systems, 2nd Edition [3]
- GAMP 5 2nd Edition [10]

These provide guidance and advice on two inter-related subjects. Indeed, the current version of USP <1058> integrates instrument qualification and computer validation for analytical equipment [8], and the integrated approach is discussed in more detail in recent publications [11-13].

- A user requirements specification must be written for both instruments and software to define the intended use and highlight which instrument will be qualified/software validated.
- Where the software application must be configured to protect electronic records generated by the system, this must be reflected in the validation documents for the application software.
- By implementing suitable controls to transfer, mitigate, or eliminate any record vulnerabilities, they can be adequately protected and ensure data integrity.

Failure to ensure that an analytical instrument is adequately qualified, or software is adequately validated means that all work in the top two levels of the Data Integrity Model above is wasted as the accuracy, quality, and integrity of the reportable results is compromised by unqualified instrumentation and unvalidated and uncontrolled software.

Assessment, remediation, and long-term solution of paper processes and computerized systems are also included in Level 1 of the Data Integrity Model, and these were required remediation actions in the Stason and Tender warning letters [14,15]. In the second eBook, we will look at process mapping and redesign as the first steps in digitalization of a business process prior to implementation and validation of a computerized system.

## COMPUTER SOFTWARE ASSURANCE

A new initiative from the FDA's Centre for Devices and Radiological Health (CDRH) is Computer Software Assurance (CSA) as a different approach to CSV. The latter was seen as generating paperwork to keep auditors and inspectors quiet rather than demonstrating fitness for intended use. This is a strange argument, as 21 CFR 211.63 has required that equipment is fit for intended use since 1978 [16].

However, CSA has opened a discussion about how some companies perform CSV and over-engineer documentation and their approaches. What is lacking is a draft guidance document from the FDA, which has been promised for over three years. Providing a scientifically sound and risk-based approach is taken to CSV. There is no need for CSA, as discussed in a separate article [17].

## BARRIERS TO LABORATORY DIGITALIZATION

Apart from senior management's unwillingness to invest in digitalization, there are three other main barriers to digitalization: hybrid systems, spreadsheets, and static data.

### What is a Hybrid System?

First, it is important to define what we mean by a hybrid computerized system. The best definition is found in the WHO guidance [18]:

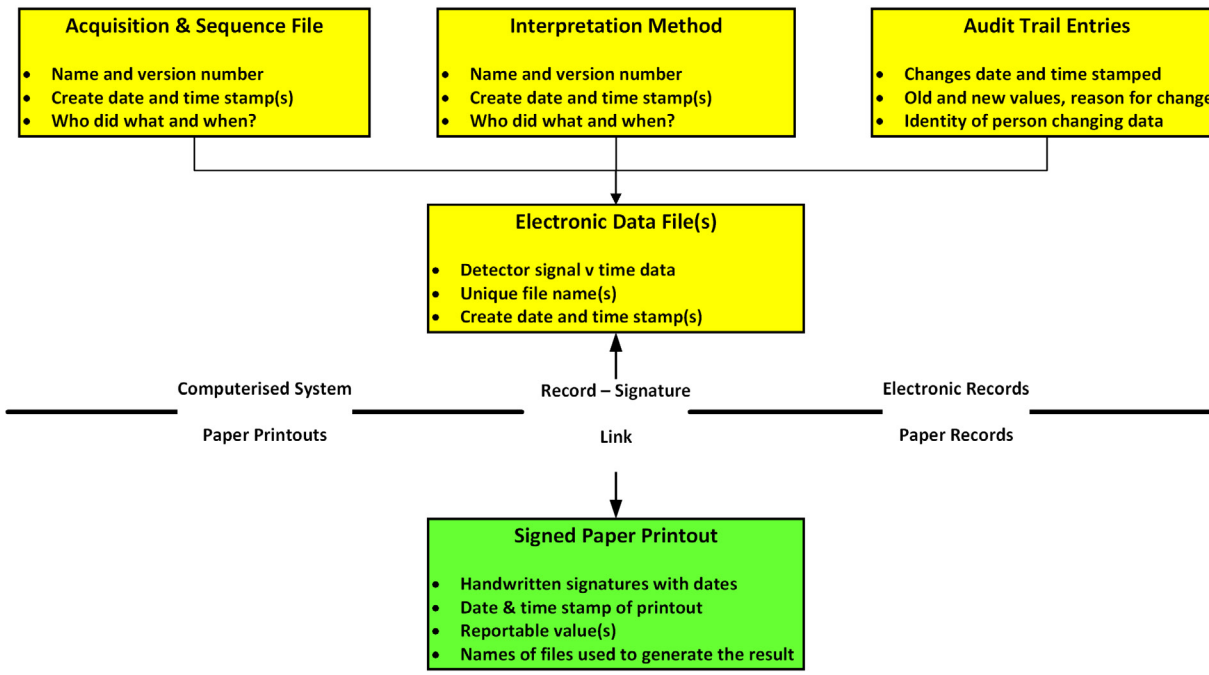
> *This refers to the use of a computerized system in which there is a combination of original electronic records and paper records that comprise the total record set that should be reviewed and retained.*

*An example of a hybrid approach is where laboratory analysts use computerized instrument systems that create original electronic records and then print a summary of the results.*

*The hybrid approach requires a secure link between all record types, including paper and electronic, throughout the records retention period.*

A hybrid laboratory computerized system is shown in FIGURE 2 [4]. There are number of electronic records within the computerized system that must be securely linked with the paper printouts that are signed by the analyst and reviewer. Often, the focus is only

**FIGURE 2:** A Hybrid System consisting of electronic records and signed paper printouts [4].



on the paper printout and not the electronic records; when, in fact, it should be the other way around. E-records are the critical data and signed paper printouts are only a small part of the records. You will recall the BBC Group warning letter earlier, where one of the citations was for the loss of three years of chromatographic data [19]. Paper records alone are not acceptable for any hybrid system. We will now discuss one specific hybrid system: the ubiquitous spreadsheet.

**Spreadsheets**

Available on almost every workstation in a laboratory, a spreadsheet application is the gift that keeps on giving to inspectors and auditors. They can be unvalidated [19] or validated with calculation errors [20], but the main issue is that spreadsheets are hybrid systems that rely on manual data input with associated transcription error checking. If the resultant file is not saved, this is a failure to collect complete data, as required by 21 CFR 211.194(a) [16]. If the electronic file is not saved and a transcription error is found in the paper printout, a spreadsheet Groundhog Day begins. All data is inputted again and again [21,22].

Analysts like spreadsheets but do not consider the business process. Manual input is error prone and negatively impacts business efficiency, as errors must be corrected and then rechecked. Hybrid systems are a major barrier to digitalization that we will continue discussing in the next section.

## ELIMINATE HYBRID SYSTEMS

Working with the existing hybrid systems in a laboratory is the WORST possible situation to be in. The laboratory must manage incompatible media formats: paper printouts synchronized with all the corresponding electronic records, including audit trail entries, over the record retention period. This is recognized by both the WHO [18] and PIC/S guidance documents that discourage the use of hybrid system, the latter states in Section 9.10.1:

> *Hybrid systems require specific and additional controls in reflection of their complexity and potential increased vulnerability to manipulation of data.*
>
> *For this reason, the use of hybrid systems is discouraged and such systems should be replaced whenever possible [23].*

Therefore, if the systems currently used in hybrid mode have electronic signature capability, this functionality should be enabled to eliminate paper printouts. Inspectors and auditors will inevitably view the electronic records within a hybrid system rather than the associated paper printouts.

## WHY ARE YOU STILL BUYING HYBRID SYSTEMS?

I could have entitled this sub-heading, “Why are Suppliers Still Selling Hybrid Systems?”. However, as suppliers respond to market forces, it is the responsibility of customers to put pressure on suppliers to design adequate systems for today’s data integrity world. Laboratories who have assessed and remediated current systems are perpetuating the problem when new systems are

purchased, as they typically include:

- Standalone workstations collecting data
- Hybrid operations generating paper printouts
- Data stored in directories created in the operating system rather than in a database

PIC/S PI-041 data integrity guidance notes in Section 9.1.4:

> *The processes for the design, evaluation, and selection of computerised systems should include appropriate consideration of the data management and integrity aspects of the system.*
>
> *Regulated users should ensure that vendors of systems have an adequate understanding of GMP/GDP and data integrity requirements, and that new systems include appropriate controls to ensure effective data management [23].*

Therefore, it is the responsibility of the laboratory to undertake sufficient due diligence to evaluate not just the analytical instrument and the associated software for its intended use but also the data integrity controls within the application. In addition, the vendor of the system must be assessed to ensure that they understand the regulatory and data integrity environment that laboratories operate in now. An analysis of over 100 483 warning letter citations showed that 40% of them could have been prevented by a laboratory performing adequate due diligence when evaluating the software [24]. A vendor's argument that the pharmaceutical industry represents only a small proportion of their sales revenue is not an adequate justification for them failing to implement technical controls in their software. Many of the requirements to meet the technical requirements of regulations are good science and ensure records are complete, consistent and accurate. They are important for patent protection as well as data integrity. This selection process must not be undermined by senior management or the purchasing department selecting a different system based solely on price. The alternative is that you perpetuate the Hidden Factory in your laboratory, discussed in the second eBook, by buying hybrid systems.

## UNDERSTANDING STATIC DATA IN THE CONTEXT OF DIGITALIZATION

Data generated during the course of analysis can be divided into static and dynamic. TABLE 1 presents the definitions of static and dynamic

**TABLE 1:** Static and Dynamic Data

| Static Data | Dynamic Data |
|---|---|
| Static is used to indicate a fixed-data record. | Dynamic means that the record format allows interaction between the user and the record content. |
| Paper record or an electronic image | A dynamic chromatographic record may allow the user to change the baseline and reprocess chromatographic data so that the resulting peaks may appear smaller or larger.<br><br>It also may allow the user to modify formulas or entries in a spreadsheet used to compute test results. |

data, with examples quoted from Question 1(d) from the FDA Data Integrity guidance [25]. The definition of static data gives the impression that nothing happens after the record is created and it remains immutable for the record retention period. In contrast, dynamic data requires interpretation by an analyst to obtain the reportable result. As you can see from Table 1, chromatography data and spreadsheets are examples of dynamic data compared with static data such as a balance printout or an observation result such as colour, etc.
Static data are a barrier to digitalization from two perspectives:

1. Static data are fixed records typically written or printed on paper which, obviously, is difficult to share.
2. Later in a business process, the static data can become dynamic data (e.g., a sample or reference standard weight can be manually input into an informatics application). If a mistake is made, it must be corrected and is dynamic data.

Creating such static records that are later typed into an application is inefficient, slow, and error prone. Instead, laboratories should automate the complete process to eliminate the static data and enable sharing of all analytical data for review. Furthermore, the focus of printouts from analytical instruments is inconsistent with both US and EU regulations for keeping current with technology [16, 26, 27].

However, before we can start digitalizing the laboratory, we must consider the analytical data life cycle and the variety of data that we must manage in the laboratory. Without this understanding, assumptions can be made that all data are the same, when different analyses produce different data and records.

**References:**


1. *ICH Q10 Pharmaceutical Quality Systems*. 2008, International Conference on Harmonisation: Geneva.
2. *EudraLex - Volume 4 Good Manufacturing Practice (GMP) Guidelines, Chapter 1 Pharmaceutical Quality System*. 2013, European Commission: Brussels.
3. *R.D.McDowall, Validation of Chromatography Data Systems: Ensuring Data Integrity, Meeting Business and Regulatory Requirements* Second Edition ed. 2017, Cambridge: Royal Society of Chemistry.
4. R.D.McDowall, *Data Integrity and Data Governance: Practical Implementation in Regulated Laboratories*. 2019, Cambridge: Royal Society of Chemistry.
5. *USP General Chapter <1220> Analytical Procedure Lifecycle*. 2022, United States Pharmacopoeia Convention Inc: Rockville.
6. *ICH Q14 Analytical Procedure Development, Step 2*. 2022, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Geneva.
7. *ICH Q2(R2) Validation of Analytical Procedures, Step 2*. 2022, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Geneva.
8. *USP General Chapter <1058> Analytical Instrument Qualification*. United States Pharmacopoeia Convention Inc.: Rockville, MD.
9. *GAMP Good Pracice Guide A Risk Based Approach to GXP Compliant Laboratory Computerised Systems, Second Edition* 2012, Tampa, FL: International Society for Pharmaceutical Engineering.

10. *Good Automated Manufacturing Practice (GAMP) Guide, Version 5.* 2nd ed. 2022, Tampa, FL: International Society for Pharmaceutical Engineering.
11. P.Smith and R.D.McDowall, *Data Integrity and USP <1058>: Part 1 Specifications and Suppliers.* LCGC Europe, 2018. 31(7): p. 385–389.
12. P.Smith and R.D.McDowall, *Data Integrity and USP <1058>, Part 2: OQ Supervision and Execution.* LCGC Europe, 2018. 31(9): p. 504–511.
13. P.Smith and R.D.McDowall, *Data Integrity and USP <1058>: Part 3: Monitoring and Requalification.* LCGC Europe, 2019. 32(1): p. 28-32.
14. *FDA Warning Letter Stason Pharmaceuticals, Inc.* 2020; Available from: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/stason-pharmaceuticals-inc-604889-07082020.
15. *FDA Warning Letter Tender Corporation* 2020; Available from: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/tender-corporation-599789-07232020.
16. *21 CFR 211 - Current Good Manufacturing Practice for Finished Pharmaceuticals.* Federal Register, 1978. 43(190): p. 45014 - 45089.
17. R.D.McDowall, *Does CSA Mean "Complete Stupidity Assured?".* Spectroscopy, 2021. 36(9): p. 15-22.
18. *WHO Technical Report Series No.996 Annex 5 Guidance on Good Data and Records Management Practices.* 2016, World Health Organisation: Geneva.
19. *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.
20. *FDA Warning Letter Tismore Health and Wellness Pty Limited* 2019; Available from: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/tismor-health-and-wellness-pty-limited-588104-12052019.
21. R.D.McDowall, *Are Spreadsheets a Fast Track to Regulatory Non-Compliance?* LCGC Europe, 2020. 33(9): p. 468–476.
22. R.D.McDowall, *Spreadsheets: A Sound Foundation for a Lack of Data Integrity?* Spectroscopy, 2020. 35(9): p. 27-31.
23. *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.
24. P.A.Smith and R.D.McDowall, *Analysis of FDA Infra-Red 483 Citations – Have You a Data Integrity Problem?* . Spectroscopy, 2019. 34(9): p. 22-28.
25. *FDA Guidance for Industry Data Integrity and Compliance With Drug CGMP Questions and Answers* 2018, Food and Drug Administration: Silver Spring, MD.
26. *Facts About the Current Good Manufacturing Practices (CGMPs).* 2021; Available from: https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps.
27. *European Union Directive 2001/83/EC on Medicinal Products for Human Use.* 2001, European Commission: Brussels.



**R D McDowall, PhD**

Director

R D McDowall Limited

Agilent OpenLab

# Get Proactive about Data Integrity in Your Lab

## Learn how to secure and manage data with Agilent OpenLab software

Your lab results are only as reliable as the data they're based upon. Yet the complexities of safeguarding and managing lab data today can be daunting, no matter which industry you're in.

Visit our site and learn how to take a proactive approach to data integrity.

www.agilent.com/chem/data-integrity

- Improve quality
- Manage records
- Secure data
- Be audit ready
- Stay current
- Validate systems

Agilent

Trusted Answers


# A Flexible Analytical Data Life Cycle

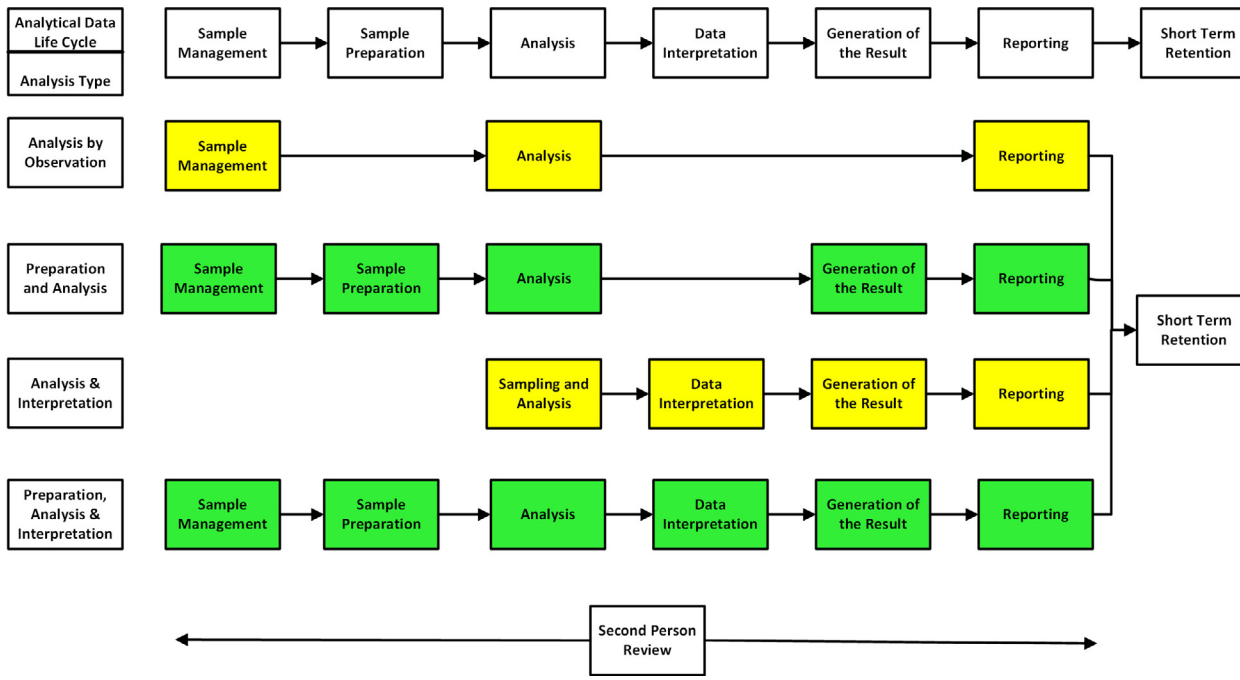
**SUMMARIZING** the life cycle so far, we have:

- Two Phases: active and inactive
- Four Elements: Control, Process, Review and Retain

We now need to consider the flexibility of the process element representing the most interesting portion of the data life cycle: analytical science! **FIGURE 1** [1] shows the following components of the process as:

- Sampling and sample management
- Sample preparation
- Instrument and data system set up
- Sample analysis including standards, blanks etc.
- Data processing
- Calculation of the reportable result(s)
- Reporting

**FIGURE 1:** Phases required by different analytical techniques of a flexible analytical data life cycle [1].




This seems to be a reasonable process flow. At each stage, you can identify the data and records that must be captured, integrated, calculated and transformed. When expanded fully, this process should define the analytical data life cycle for an analysis.

## ONE SIZE FITS ALL?

However, does a one-size analytical data life cycle fit all? Do all analytical procedures require all stages of the process presented in the section above? Let us consider the following scenarios:

- On-line or in process analysis may not require sample management or sample preparation
- If the sample is liquid, sample preparation may not be required
- Qualitative analysis will not require calculation of results

Therefore, any analytical data life cycle needs to be flexible and scalable to accommodate different analytical procedures, rather than force all into a one-size-fits-all approach.

The analytical data life cycle in FIGURE 1 is a better approach but is still not perfect and needs to be refined further. In this respect, different analyses should have a variant of the analytical data life cycle to reflect what happens in a regulated laboratory. To

illustrate this, we will consider four different analytical procedures that are typical in the pharmaceutical industry:

1. **Analysis by Observation**
   Typically, a sample will be taken, and an aliquot is transported to the laboratory for a test based on observations such as color, appearance or odor. As such, sample preparation, data interpretation and generation of the result are not needed, as the analysis is the reportable result. This means that for these types of analyses, a simpler and more appropriate data life cycle is indicated.
2. **Sample Preparation and Instrumental Analysis**
   Typified by a loss on drying (LOD) analysis, there is a slightly more complex data life cycle. Sample management is applicable, but the sample preparation is relatively minimal and is restricted to weighting the sample within the limits specified by the pharmacopeial method. The analysis consists of weighing the sample before and after heating and calculating the percentage loss. As such, there is no requirement for interpretation of data.
3. **Combined Instrumental Analysis and Data Interpretation**
   Here, the sample management and sample preparation tasks of the analytical data life cycle are not required. This is typified by NIR identity analysis. Instead, the sampling and analysis phases are combined into one, as the analytical instrument is connected directly into an analytical process when a shipment of material is received in the warehouse. The spectrum of the sample is compared to a composite spectrum in a spectral library.
4. **Instrumental Analysis with Data Interpretation**
   The whole analytical data life cycle is applicable to instrumental analysis. This is typified by a chromatographic analysis that requires sample management and preparation, set of the instrument, acquisition of the data and calculation of the reportable result.

Of note for the discussion on digitalization is that analyses 1 and 2 typically generate static records. Therefore, we need to consider how to capture these data and improve the two business processes. We will return to the discussion on static data, which was highlighted earlier as a barrier to digitalization.

## HOW STATIC ARE STATIC DATA?

Back to the laboratory bench. Imagine you are weighing either sample aliquots or a reference standard on an analytical balance and the weighing sequence (e.g., vessel weight, tare, material weight) is printed out. It is generally accepted that this is a static record, where the balance printout is attached to a laboratory notebook or analytical batch record. Indeed, the 2021 PIC/S guidance in section 8.9.1 states:

> *Some very simple electronic systems, e.g. balances ….which do not store data, generate directly-printed paper records. These types of systems and records provide limited opportunity to influence the presentation of data by (re-)processing, changing of electronic date/time stamps. In these circumstances, the original record should be signed and dated by the person generating the record and information to ensure traceability, such as sample ID, batch number, etc. should be recorded on the record. These original records should be attached to batch processing or testing records [2].*

This approach is repeated in the FDA data Integrity guidance in Question 10:

> *Is it acceptable to retain paper printouts or static records instead of original electronic records from stand-alone computerized laboratory instruments, such as an FT-IR instrument?*
>
> *A paper printout or static record may satisfy retention requirements if it is the original record or a true copy of the original record (see §§ 211.68(b), 211.188, 211.194, and 212.60). During data acquisition, for example, pH meters and balances may create a paper printout or static record as the original record. In this case, the paper printout or static record, or a true copy, must be retained (§ 211.180) [3].*

The stated regulatory expectation of both the PIC/S and FDA guidance documents for simple analytical instruments is for paper printouts that are attached to an analytical batch record or a laboratory notebook. Whilst there is limited ability to interfere with the printout, without an audit trail and e-records, weighing can be repeated until the "right" result is obtained.

However, if we are considering laboratory digitalization, this is not the right approach to take.

## STATIC DATA ARE INTEGRAL TO ANALYTICAL PROCEDURES

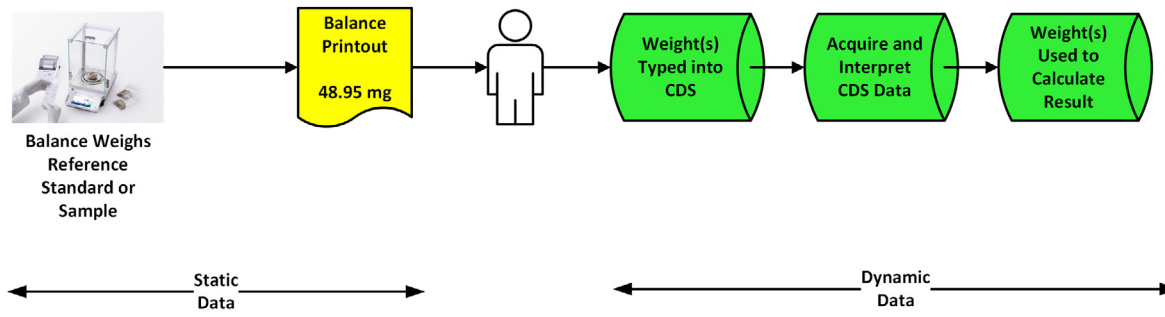
Simple instruments, such as balances, generate critical data that are used as inputs to analytical procedures such as quantitative chromatographic analysis, e.g.:

- Determination of purity
- Stability testing
- Impurity determination
- Residual solvent measurement
- Etc.

Here, static data becomes an integral component of a dynamic data process.

However, many laboratories still have inappropriately designed data processes for the small instruments that generate critical data on paper printouts. This is compounded by manually entering the weight into a computerized system, or worse, a spreadsheet, resulting in transcription error checking by the reviewer.

**FIGURE 2:** Converting static data into dynamic data.




We can look at this situation further in FIGURE 2. On the left of the diagram is the generation of a static data record: the balance printout. On the right, weights of samples and standards are manually entered into a CDS that generates dynamic data used to generate the reportable result. Here, we can see the conversion of static data into dynamic data. If the analyst entering weights into CDS mistypes a value that must be corrected later with a corresponding audit trail entry, what was static data on the printout is now dynamic data in the CDS.

This poses a key question: Why make data static first, only to make it dynamic later?

## IS REGULATORY GUIDANCE CORRECT?

The heading poses a fundamental question: Where is the event horizon when considering if data are static or dynamic? Consider the following situation:

- **Static Data:** Analytical balance and printout in isolation:
  Weigh sample + print result = static data

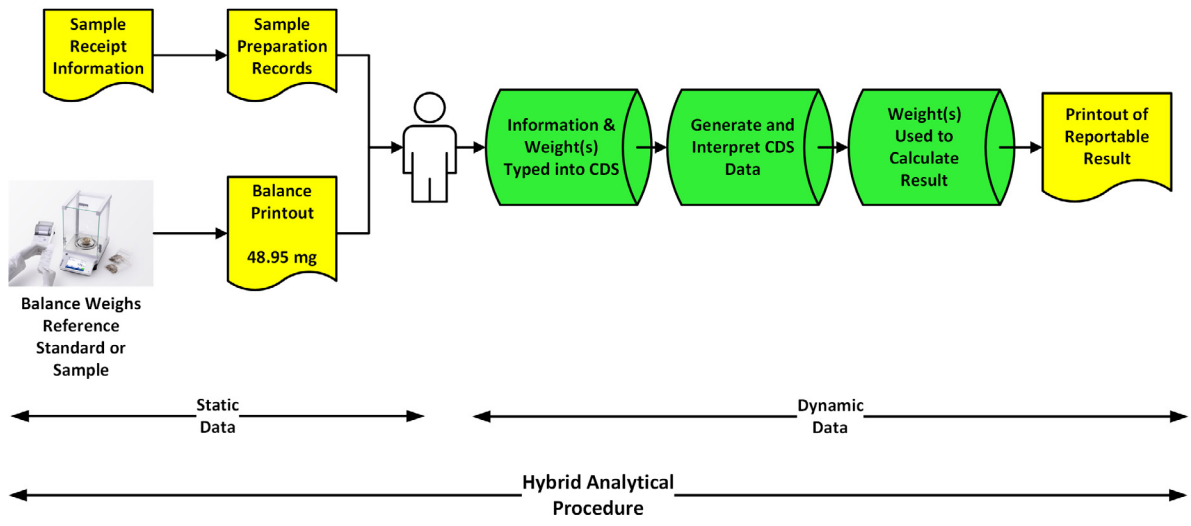
- **Dynamic Data:** The balance and sample weight are integral parts of an overall CDS analytical procedure:

  Weigh sample + print result + type weight into CDS + acquire data + generate result = dynamic data

The dynamic equation only takes a high-level view of an analytical procedure. What also must be considered are all the contextual meta data generated throughout the process.

The records generated are a mixture of paper printouts (in yellow) and electronic records (in green), and yet more paper as shown in FIGURE 3. Whilst there may be some static data records generated at the start with sample preparation and the balance printout,

**FIGURE 3:** An analytical procedure with hybrid records.




the overall process generates dynamic data. We now have an analytical procedure that generates hybrid records.

Even if the instrument data system were to use electronic signatures, only one item of paper would be eliminated (the paper printout on the right of FIGURE 3). A hybrid analytical procedure still remains. FIGURE 3 shows the complete record set that needs to be reviewed and archived, but the problem is that there are several static paper records plus electronic records.

Are hybrid analytical procedure records an adequate situation to be in? The answer is an unequivocal NO.

We now need to consider the business drivers for digitalization of the laboratory.

**References:**


1. R.D.McDowall, *Data Integrity and Data Governance: Practical Implementation in Regulated Laboratories*. 2019, Cambridge: Royal Society of Chemistry.
2. 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.
3. *FDA Guidance for Industry Data Integrity and Compliance With Drug CGMP Questions and Answers* 2018, Food and Drug Administration: Silver Spring, MD.



**R D McDowall, PhD**

Director

R D McDowall Limited

Agilent OpenLab

# Faster Turnaround Times, Higher Work Quality. Pick Both.

## Eliminate trade-offs and transform your lab operations with OpenLab Software

There is no reason to settle when it comes to operational efficiency. With OpenLab Software, you can transform the productivity and quality of your analytical workflows simultaneously.

Get the full range of advanced capabilities you need to radically improve every phase of the workflow—from sample submission to data acquisition to data analysis, reporting, and data management. Get the details by visiting our website—then contact us for a free consultation.

www.agilent.com/chem/transform-your-lab

Sample submission

Reporting

Data acquisition

Data management

Data analysis

Agilent

Trusted Answers

DE44487.6494560185


# Business Drivers for Digitalization

I have left this section for last, as it serves as a bridge between this eBook and the second. The second eBook covers the development of a strategy for laboratory digitalization that includes mapping and improving analytical processes. As a regulated industry, it is essential to comply with the applicable regulations. It does not mean to the exclusion of business efficiency and effectiveness. Digitalization can provide both regulatory compliance and business benefits; the former was discussed earlier in this eBook. We will now consider the business drivers.

## AN UNUSUAL REGULATORY GUIDANCE

We will start this discussion of the business drivers for digitalization from an unusual source: a regulatory authority data integrity guidance that we mentioned earlier. Believe it or not, the WHO 2016 guidance has one section that is very pertinent to digitalization and process improvement:

*§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]*

Let us look at this section on more detail:

- **Leverage existing technologies to their full potential:** As we have seen with the three warning letters earlier in this eBook, analytical instruments were operated in standalone mode printing paper (static records) and were not connected to informatics applications [2, 3] or instruments that have the capability to store electronic records, don't [4]. This is not confined to warning letters; laboratories use spreadsheets for calculating chromatographic system suitability test (SST) parameters that, if the manual was read, come with the application.
- **Streamline data processes:** Most laboratory processes have evolved over time and have not been designed. Paper-based processes are infinitely flexible. If there is a problem, these either add another price of paper or you need to develop a spreadsheet – problem solved! Data integrity guidance documents expect laboratories to assess their process to identify any data vulnerabilities. This is an ideal opportunity to streamline your processes and make life easier. You also must keep current.
- **Improve data management:** Removal of paper from a process coupled with technical controls to enforce working practices is an essential part of a laboratory digitalization roadmap. Automated attribution of action and contemporaneous time and date stamping generate confidence in a validated process.
- **Business process efficiency and effectiveness:** Implementing the items above will make processes efficient and effective. Or, to put things another way, this allows you to work smarter and not harder.
- **Reduce costs:** Removing human labor from a process (e.g., manual data entry and associated transcription error checks by the performer and reviewer) reduces costs. This time can be reallocated to value-added tasks within the laboratory, such as interpretation of data.
- **Facilitate continual improvement:** Digitalizing a process provides the metrics to monitor and improve it.

## BUSINESS EFFICIENCY IS IMPERATIVE

Regardless of the regulations, companies should consider digitalization from a business efficiency perspective alone. Often, QC testing is conducted at the end of manufacturing and can be seen as slowing the release of a

batch of product. If a laboratory was more efficient with the analysis and release of the Certificate of Analysis, what would be the impact on a company cash flow if every batch were released to the market one day earlier? The way to do this is to work smarter and electronically through digitalization of the laboratory and the removal of paper.

The COVID-19 pandemic has forced laboratories to glimpse into a new way of working, with some analysts working in the laboratory and others remotely. This can only work if data are electronic and not on paper.

- You can't share paper remotely.
- In an electronic environment imagine doing laboratory work remotely, such as second person review.
- Review of data and audit trail entries as well as signing results and reports can be performed remotely.
- Trending can also be performed electronically to meet the requirements of EU GMP Chapter 6.9 [5].

You can't perform these tasks with working practices that generate static data and hybrid records.

## PREREQUISITES FOR AUTOMATION

Automating a complete laboratory is not a quick fix and requires the following prerequisites to be incorporated into a strategy document:

- Active Management support
- Resources (both staff and money)
- Interpretation of regulatory requirements and effective risk management
- Process mapping and redesign
- Identifying and solving data integrity vulnerabilities
- Strategic planning for the whole laboratory coupled with quick wins 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

The next eBook will explain the process of developing digitalization strategy and help you plan how to automate your laboratory.

## WHAT COULD YOUR LABORATORY LOOK LIKE?

Looking ahead to when you have started on your digitalization journey, what could your laboratory look like?

- **Automatic data acquisition.** Instead of writing down observations and data, these would be input or captured directly into an informatics solution. Data would be automatically attributed to a named user and be time and date stamped via a trusted time source. This enhances and ensures both regulatory compliance and data integrity.
- **No hybrid systems (including spreadsheets).** Hybrid systems should not be used following the transformation

to electronic processes. Spreadsheets should be eliminated, and the calculations should be incorporated into either instrument data systems or other informatics applications.

- **Less paper to manage.** If data and records are captured, interpreted and stored electronically, there is less paper to manage. As a result, the administrative overhead of managing and reconciling uniquely numbered blank forms [1, 6, 7] is eliminated. In turn, this requires less physical storage for paper records.
- **Transcription error checking is reduced or eliminated.** In addition to less paper, direct data capture and electronic transfer means that transcription checking is reduced \ or eliminated entirely.
- **Second person review is faster.** Having data and records in one medium, and second person review is quicker.
- **Audit trail entries are reviewed by exception.** If the technical control is present and validated in an application, a reviewer should only review GMP relevant changes as highlighted by the application, as advocated by the PIC/S data integrity guidance [6], again speeding the overall review process.

## References:


1. WHO Technical Report Series No.996 Annex 5 Guidance on Good Data and Records Management Practices. 2016, World Health Organisation: Geneva.
2. FDA Warning Letter Stason Pharmaceuticals, Inc. 2020; Available from: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/stason-pharmaceuticals-inc-604889-07082020.
3. FDA Warning Letter Tender Corporation 2020; Available from: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/tender-corporation-599789-07232020.
4. 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.
5. EudraLex - Volume 4 Good Manufacturing Practice (GMP) Guidelines, Chapter 6 Quality Control. 2014, European Commission: Brussels.
6. 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.
7. FDA Guidance for Industry Data Integrity and Compliance With Drug CGMP Questions and Answers 2018, Food and Drug Administration: Silver Spring, MD.



**R D McDowall, PhD**

Director

R D McDowall Limited

# Summary

This e-Book sets the scene for how to digitalize a laboratory by considering the regulatory background, including why it is important to keep current with advances in technology, understand the costs of compliance and noncompliance as well as key FDA regulatory citations. The importance of AIQ and CSV in ensuring regulatory compliance and ensuring data integrity is critical but needs to be focused and risk based. Some of the barriers to digitalization have been discussed, leading to a flexible analytical data life cycle and the importance of eliminating 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.

We will look at the way to develop the strategy in more detail in the next eBook.

***Remember, digitizing a laboratory is a journey and not an event.***


## ABOUT THE AUTHOR

R D McDowall, PhD

Director

R D McDowall Limited


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.

DE70066402