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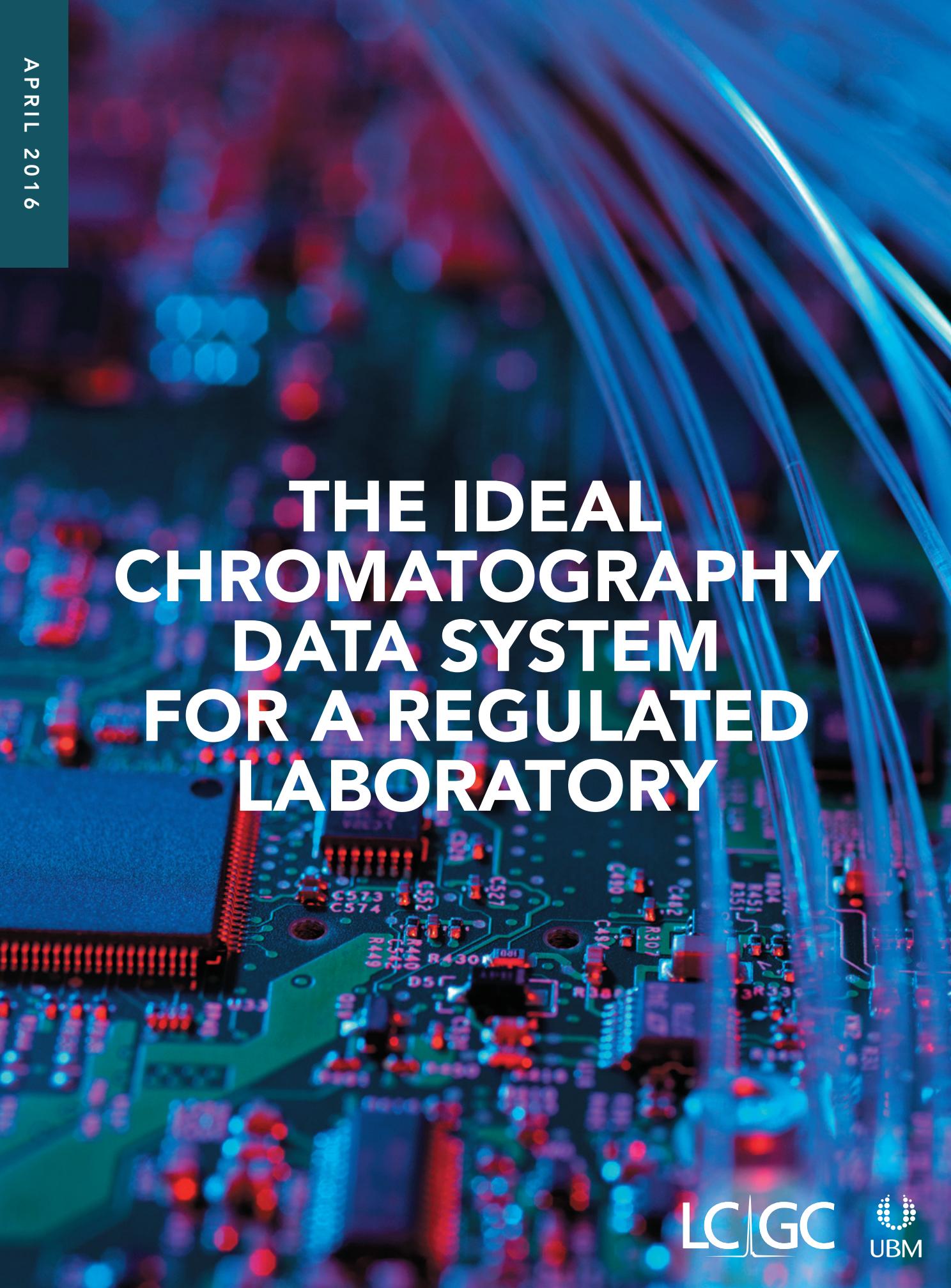

THE IDEAL CHROMATOGRAPHY DATA SYSTEM FOR A REGULATED LABORATORY

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THE IDEAL CHROMATOGRAPHY DATA SYSTEM FOR A REGULATED LABORATORY, PART I: THE COMPLIANT ANALYTICAL PROCESS

R.D. McDowall and Chris Burgess

This article is the first of a four-part series looking at what functions and features the authors believe should exist in an ideal chromatography data system (CDS) of the future, designed for use in a regulated analytical laboratory. The first part of this series sets the scene of where and how a CDS fits into a laboratory operation. In the next three parts we make 15 recommendations for improvements to the system architecture, new CDS functions to enable fully electronic workflows, and features to ensure regulatory compliance.

Chromatography is a major analytical technique, especially in a regulated analytical laboratory, where chromatographic analyses can comprise up to 80% of the total analytical workload in some organizations. Automation of chromatographic analysis (instrument control, data acquisition, integration, and reporting of results) is undertaken by a chromatography data system (CDS). Unfortunately, CDS software has been at the heart of several recent data falsification cases (1), which demonstrates that we need a more systematic and structured approach to designing the ideal CDS, so that a CDS can be used not only to improve the speed and efficiency of the chromatographic process but also to ensure regulatory compliance. The regulations we refer to in this series of articles are the *GXP* regulations, a term that includes good laboratory practice (GLP), good manufacturing practice (GMP), and to a lesser extent good clinical practice (GCP).

It is important to understand that the current versions of CDS software were designed and released before the current regulatory focus on data integrity. Even if a CDS has the features required to enable chromatographers to carry out their work electronically, many laboratories use the system manually or as a hybrid (with signed paper printouts from the associated electronic records) and in many cases coupled with the use of a

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spreadsheet to undertake calculations that should really be performed in the CDS. This approach wastes the investment in the CDS and adds cost, risk, and complexity to the overall analytical process. Furthermore, many organizations do not know when and when not to perform manual integration. Manual integration was discussed in a recent "Questions of Quality" column (2).

The four-part series will focus mainly on the functionality required in CDS software. (And we will use the term *CDS* to refer to either a traditional CDS or to a future system in which current CDS functions could form part of another informatics solution such as an electronic laboratory notebook [ELN] or laboratory information management system [LIMS].) The further development of chromatographic instruments is relatively limited and moves forward incrementally, but there are significant advances that can still be made in CDS software applications that can result in major improvements to efficiency, effectiveness, and compliance within a regulated laboratory.

Chromatography data systems automate a variety of chromatographic processes that vary from conventional high performance liquid chromatography (HPLC) and ultrahigh-pressure LC (UHPLC), conventional and capillary gas chromatography (GC), and also HPLC and GC coupled with a range of mass spectrometry (MS) detectors. Many chromatography–MS systems have CDS applications that have come from a research environment into the regulated environment, and these data systems are ill-prepared for use in a regulated laboratory because they have system architectures and features that do not necessarily ensure data integrity. The scope of this series of articles includes these chromatography data systems. The principles outlined in these articles should also be applicable to laboratories working under other quality systems such as International Organization for Standardization (ISO) 17025. Also, although this article series focuses on CDS software, the principles outlined here apply to other laboratory computerized systems.

Before we can focus on the functions of an ideal CDS, however, we need to set the scene by looking at the role and function of a regulated analytical laboratory and the role of a CDS within it. This is the scope of the first part of this series.

Role of Analysis

The purpose of analysis is to predict the properties of a batch or lot based upon a sample taken from it on a sound scientific basis or a subject concentration time profile from a nonclinical or clinical protocol. Clearly the sample must be representative of the batch, but the issue of sampling and sample management is not considered in this series of articles. Given that business and regulatory decisions are made on the basis of such a prediction, a total data quality management system must be in place

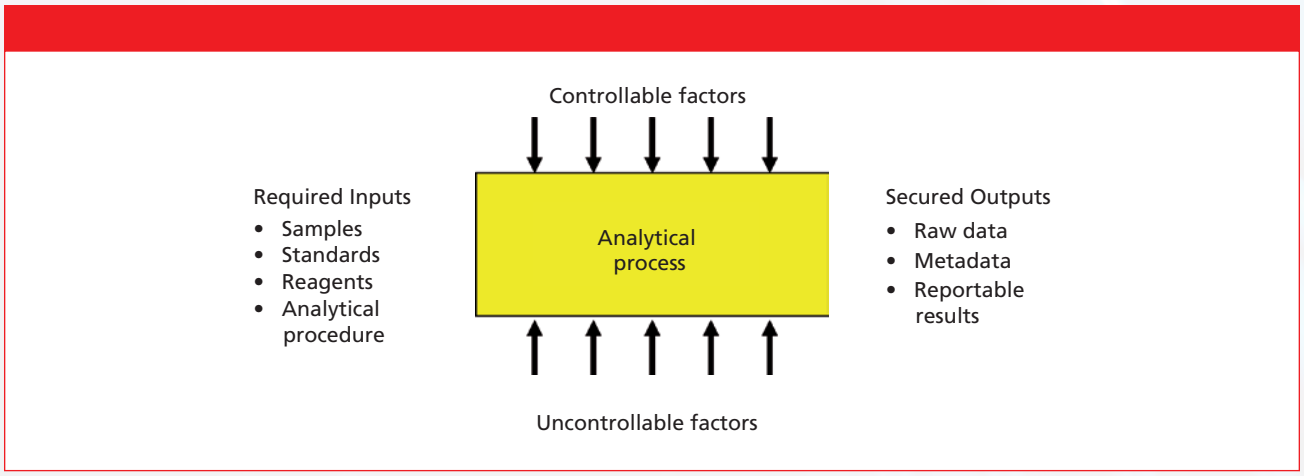

Figure 1: A basic representation of the analytical process.

to ensure the integrity and security of metrology and derived results at all stages of the analytical process.

There are a number of critical aspects of an ideal quality management system:

- It should follow a life-cycle approach based on the principles of International Conference on Harmonization (ICH) Q10 (3).
- Data acquisition must take place at or close to the point where the data are generated.
- Only electronic interfaces must be permitted; there should be no facility for making manual inputs. Therefore all systems and instruments must be interfaced and integrated together to prevent manual entry or reentry of data followed by subsequent transcription error checking (as occurs with a hybrid system).
- Full and transparent traceability of both the data acquisition and the subsequent calculation processes must be in place.
- The location of the data and the associated metadata and subsequent metadata must be known and secured to enable rapid retrieval.
- Data and metadata must be secure at the time of capture, so that changes can only be made through the application software, with corresponding audit trail entries.

The primary focus of any process control strategy is always the prevention of error from controllable factors. The detection of error from uncontrollable sources is a secondary but important consideration, which we will explore below.

The Analytical Process

The basic analytical procedure is shown in **Figure 1**. Inputs consist of samples, reagents, standards, and a specific analytical procedure with secured outputs of raw data, metadata, and reportable results. Throughout the execution of any analytical procedure there are controllable

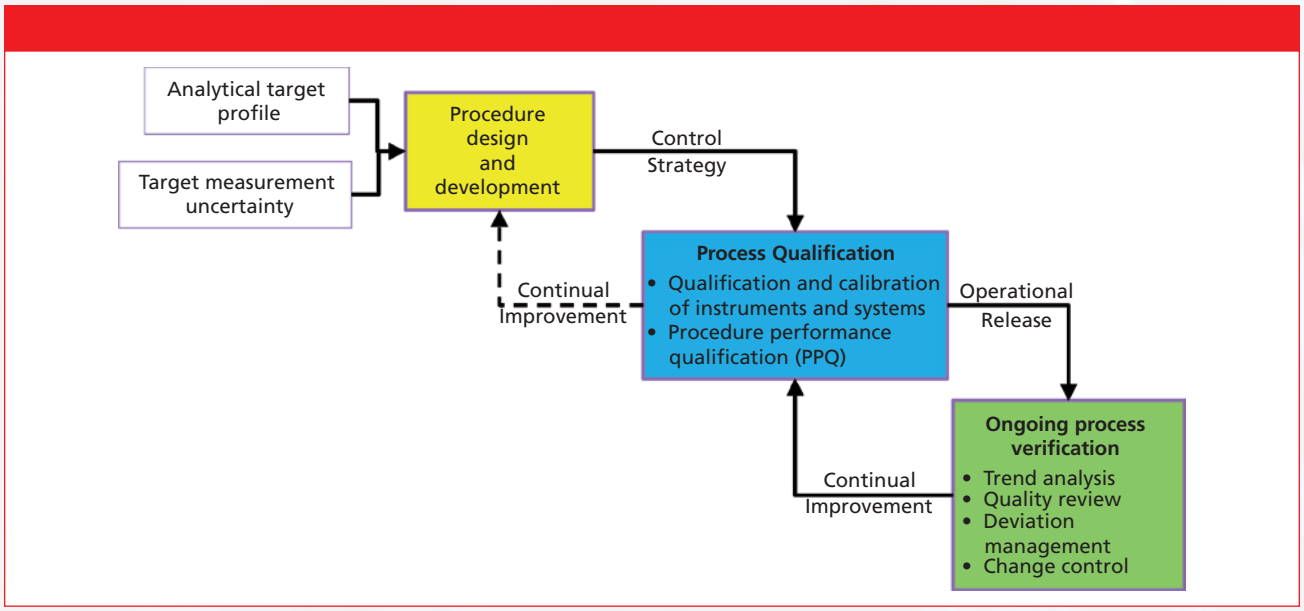

Figure 2: USP proposed approach to analytical development and validation (updated from reference 6).

and uncontrollable factors to consider.

The basic representation illustrated in **Figure 1** is simplistic, however. There are two types of life cycles in the use of an analytical procedure: the within-procedure life cycle and the between-procedure life cycle.

The within-procedure life cycle is short term and relates to the performance of the analytical process for an individual analytical measurement sequence. The between-procedure life cycle relates to ongoing verification of a state of control while the procedure is in routine operation and covers monitoring of its performance and changes in terms of time-related shifts and drifts in analytical response. Data from the within-procedure and between-procedure life cycles should be trended (4) to obtain an overview of how an individual procedure is performing over time.

Such a life-cycle concept is consistent with the core needs of ICH Q10 (3) and the Food and Drug Administration (FDA) process validation guidance (5). The key elements of these two documents are as follows:

- Management responsibility
- Understanding and improvement of process performance and product quality
- Continual review and improvement of the pharmaceutical quality system itself

A recent article in *Pharmacopeial Forum* from a USP Expert Committee has proposed a life-cycle approach to development and verification of an analytical procedure (6) and is shown in **Figure 2.** This approach starts with an analytical target profile (ATP) that specifies the performance of the required procedure in relation

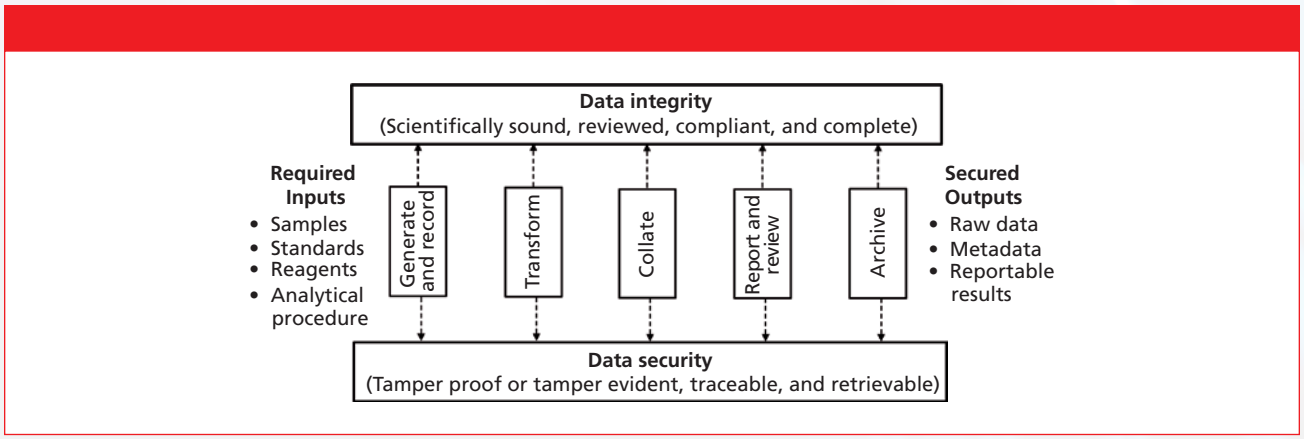

Figure 3: Concept of the "analytical factory."

to a target measurement uncertainty amongst other factors. That is to say, the reportable result definition is fit for its intended purpose with respect to a given specification. Crucially, the ATP does not specify the metrological method to be used, only the performance attributes required. An overview of this approach was discussed in a recent "Questions of Quality" column (7). The main change is the inclusion of method development within the scope of analytical procedures where previously it has been excluded, such as in ICH Q2(R1) (8,9).

However the majority of analytical procedures require a degree of specificity (selectivity), and that usually indicates the use of separation techniques such as chromatography. Therefore, if chromatography is to be used for an analytical procedure, any CDS to be used in a regulated laboratory needs to have the functionality to automate this development, qualification, and verification process effectively.

The "Analytical Factory"

The analytical procedure resides within a controlled quality managed laboratory environment: the "analytical factory," which is shown in **Figure 3.**

In this figure, the analytical procedure is broken down into the main stages needed to convert the inputs into outputs. Here, the input types are the same as in **Figure 1**, but we show the process stages familiar to readers—such as "generate and record" (data acquisition), "transform" and "collate" (interpretation), and "report and review"—in more detail. Finally, there is the need for secure and complete delivery of the reportable results. Throughout this process of the analytical factory is the requirement for two main constraints in the process: data integrity and data security. When we mention *data* we include the associated metadata that put the data in context (this is part of the *complete data* referred to by FDA regulations [10]). What **Figure 3** does not show is the

formal destruction of records after the appropriate record retention period has expired.

Metadata are for assessing data integrity. Metadata permit a result to be put into a context; a better term than *metadata* might be *associative* or *contextual data*. The March 2015 Data Integrity Guidance published by the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) has definitions of *data, metadata,* and *primary record*. We have written a critique of the definition of *primary record*, preferring a definition of *primary analytical record.* (That critique is due for publication in September 2015 [11]). Metadata allow unambiguous definition of the conversion of raw data to reportable values. For example, if presented with a result of 7.0 there is no information about the context of it. Just some of the questions that could be asked are as follows:

- What are the units of measurement?
- What does the result relate to? Does it relate to a batch or experiment number? Or to a stage of manufacturing?
- How was the result obtained? For example, what were the data acquisition method, integration method, instrument control method, sequence file, and any post-run calculations?
- How were the data generated? What instrument, column, and reference standards were used? Who was the analyst?
- What audit trail entries have existed during the analysis, especially around changes and deletions of data? For example, who made the change? What were the original and new values? What was the date and time stamp of the change and reason for the change?

Thus, metadata put an analytical result in context and are critical for ensuring data integrity.

It is important to consider how an analytical procedure relates holistically to the individual components that are controlled and uncontrolled, as suggested by **Figure 1**. More detail of these two sets of factors is shown in **Figure 4**, along with their context within an overall quality management system (QMS).

The inputs and outputs shown in **Figure 4** are the same constituents as shown in **Figures 1** and **3** but the factors affecting their integrity and security are further defined. However, the outputs can also be broken down into further detail covering data and the associated contextual metadata that will be used to generate the output of signed reportable results. Currently, the reportable results can be either the homogeneous electronically signed electronic records or the hybrid of electronic records with signed paper printouts.

The controlled factors are items such as procedures, qualified instruments, validated software systems, validated analytical procedures, and qualified and trained staff. For such factors, a control

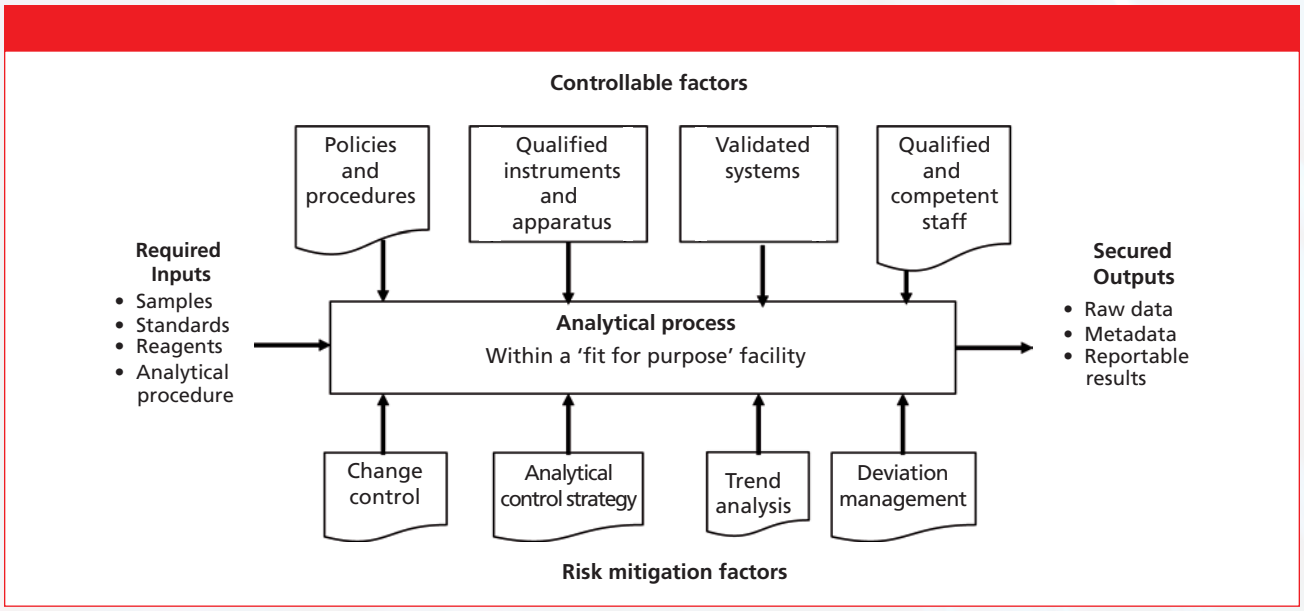

Figure 4: Achieving the concept of the analytical factory in a regulated laboratory.

strategy is required. Uncontrolled factors include deviations from procedures, instrument failures, software and system failures, method drift and uncontrolled changes to analytical procedures, and finally human error. For these factors, an effective detection system is necessary, coupled with appropriate change control procedure and validation where necessary.

An ideal laboratory informatics package of the future should cover the entire holistic analytical life cycle as far as is practically possible without need for additional external systems. Because such a system currently does not exist, we are currently left with an analytical informatics jigsaw puzzle.

Data Integrity Control Strategy

In addition to the analytical procedure life cycles that we have discussed, there also needs to be a control strategy to ensure data integrity within the CDS, as shown in **Figure 5**. Note that **Figure 5** is aligned and consistent with **Figure 3**.

The data integrity control strategy must be integrated into the analytical procedure life cycle. Such integration will provide a mechanism for ensuring that the required data checks are carried out automatically by the CDS as the individual stages of an analytical procedure are executed and will provide evidence to demonstrate that a given procedure is in a state of control.

Summary

Here in the first of this four-part series we have looked at the scope of an ideal chromatography data system or laboratory informatics solution of the future. In addition, there need to be interfaces with other instruments such as analytical balances for direct data –––

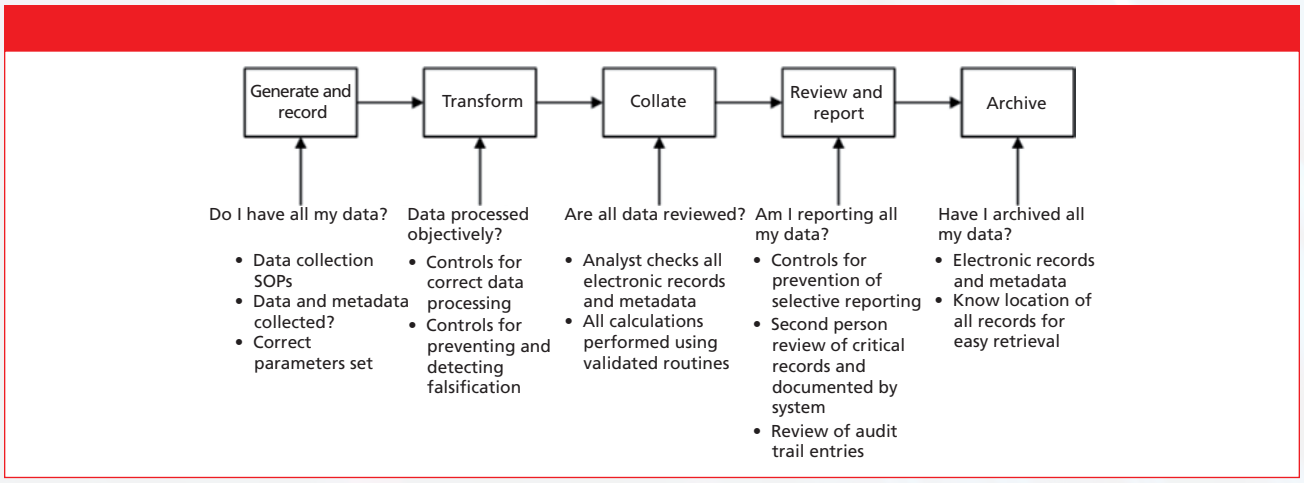

Figure 5: Data integrity control strategy for a CDS in a laboratory with fully electronic processes (adapted from M. Cahilly).

acquisition of sample weights into the sequence file to eliminate manual entry and second-person checks of such data.

However, as the focus of this series of papers is the ideal CDS of the future, the remaining parts of this series will only consider an electronic solution: an electronic process that generates electronic records that are signed electronically. The first step in this discussion, in the next article in this series, will consider the architecture of an ideal CDS. Future technical and regulatory-compliant systems will require enhanced functionality to ensure data integrity and security.

Acknowledgments

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Data Integrity in Pharma QC Labs

What You Need to Know

ON-DEMAND WEBCAST

Aired February 11, 2016

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Data integrity problems in pharmaceutical quality control laboratories are driving more regulatory action than ever before. It is obvious that something has changed to drive all this activity. There is plenty of information available, but much of it seems to confuse or frustrate rather than clarify or help. In this webinar, we will provide clarity, dispelling confusion by looking at the facts, based on a study of available resources and direct interactions with FDA staff and their consultants. You'll learn from Loren Smith, Agilent's software compliance expert and a UC Berkeley instructor with 25 years of regulated software experience, how to put the current enforcement environment in historical context, and to apply critical thinking skills to what you hear or read regarding data integrity. You'll also learn how to evaluate your current laboratory software and associated processes against these new expectations, as well as how vendors are redesigning laboratory software to help you respond to these new realities.

Key questions that indicate you should tune in to this web seminar:

- Do I understand what the new wave of data integrity enforcement means?
- Are my laboratory software and processes ready for the increased scrutiny?
- Do I understand what my responsibilities are for ensuring that both my vendor's software and my organization's processes will ensure data integrity?

After this webinar, you should be able to:

- Articulate the drivers behind the "new" data integrity regulatory enforcement actions
- Communicate the current interpretations of existing regulations
- Understand a methodology to evaluate your laboratory software

Who Should Attend

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THE IDEAL CHROMATOGRAPHY DATA SYSTEM FOR A REGULATED LABORATORY, PART II: SYSTEM ARCHITECTURE REQUIREMENTS

R.D. McDowall and Chris Burgess

Here in the second part of this series, the key system architecture requirements for a chromatography data system (CDS) in a regulated environment are discussed.

In the first article in this series (1), we looked at the role of the laboratory and discussed the concept of the analytical factory together with the controllable and uncontrolled factors influencing the analytical process. In addition, we looked at the requirements for ensuring data integrity throughout the analytical process. In this second installment, we start by defining in more detail the requirements for the future of chromatography data systems (CDS) in a regulated laboratory. Specifically, we discuss the overall system architecture for a compliant CDS in a regulated laboratory. There are a number of requirements that, in our view, a system needs to meet before a CDS can be considered to be capable for operation in a regulated laboratory.

Where Are We Now?

Current chromatography data systems come in a variety of shapes and sizes and the choice available to a laboratory will depend on the overall system size and available budget. There are three possible CDS configuration options (2):

- A standalone workstation controlling two or more chromatographs
- A standalone workstation controlling a single chromatograph including liquid chromatography–mass spectrometry (LC–MS) or gas chromatography (GC)–MS instruments
- Networked CDS system controlling multiple instruments in one or more laboratories

What Do We Need?

In our view, five main requirements are essential for a CDS operating in a regulated environment:

- Networked CDS
- Data management via a database
- Independent IT support
- Ability to interface to other instruments

and systems
- Nonproprietary data file formats including the metadata

We will discuss each one of these in the following sections.

Networked CDS Architecture

Let us be very clear that, in our opinion, for regulated analysis standalone workstations are not fit for purpose and should not be used. Only a networked CDS architecture solution should be considered. Let's look at the rationale for our position, in general:

- Standalone workstations have a problem with resource contention—for example, access to the system by different users at the same time. When data are being processed, the same workstation cannot typically be used to set up another analysis, which can reduce the throughput of the system.
- Furthermore, if during an overnight run the workstation is left unattended, it might be possible for someone to make changes that are attributed to the user who initiated the run and who may not be in the laboratory when the changes were made.
- Data can be subject to manipulation as evidenced by the number of warning letters (3).
- There is a single point of failure with the workstation hard drive, coupled with the potential loss of regulated data.

So, from the perspectives of regulatory compliance and practical use of the system, a networked CDS solution is the only option that should be considered for regulated laboratories. This statement applies even if only a single chromatograph is used. With a networked system, data can be acquired on one instrument, but processed on a different workstation in an office because the data are available via a central server. In addition, a networked CDS has one or more data servers located in the laboratory to buffer data, add resilience, and avoid data loss.

Therefore, for resilience, result processing, and review independence a networked architecture is preferred to a single workstation.

Even for a small laboratory working in a regulated environment, the CDS must be networked. Data should be acquired directly to a secure network server that is regularly backed up by the IT department. Using the currently available technology, a virtual network server, rather than a physical server, could be used to store CDS data on a network even for a single instrument. There needs to be adequate redundancy and resilience in the physical hardware platform on which the virtual server runs to reduce data loss. Today, this redundancy is achieved in CDS with the incorporation of a data server in the laboratory to buffer data in case the network is unavailable; this practice should be continued in the future.

Data Management via a Database

To ensure integrity, all data generated during any analysis must be stored safely and securely to prevent deletion, either deliberately or accidently as well as track all changes made to the data by authorized personnel. Therefore, the second architectural requirement for a CDS operating in a regulated laboratory is the need for all data to be managed via a database. Data files stored in directories in the operating system are not fit for purpose in a regulated environment. The reason for this lack of fitness has been shown by numerous warning letters regarding noncompliance and falsification through deletion of unwanted files via the operating system (3). In fact, one way inspectors will demonstrate this is to ask for a file to be created by a chromatograph and then ask a user to attempt to delete the file via the operating system.

The main reasons for incorporating a database in the system are to

- Manage all chromatographic data and associated contextual metadata
- Provide secure and encrypted storage of chromatographic data (4)
- Provide a secure and encrypted audit trail that is independent of the data files
- Have the ability to monitor, trend, and manage chromatographic data effectively across analytical runs (5)

A database is not simply an add-on to an existing CDS, but needs to be integrated and designed from first principles. You might argue that this is a draconian approach, but there are, sadly, numerous examples of falsification using operating system files. Prevention is always better and cheaper than the cure. In addition, so much mitigation is required to secure flat files that the database is a simpler solution once adequate control of data is considered.

However, some CDS systems on the market use operating system directory structures to store data, so if you insist on using a flat file structure the following issues need to be managed:

- The relationship between records must be embedded, so if files are separated the links can be established between records.
- Files must be protected from modification, copying, or deleting by unauthorized personnel immediately as they are written onto a storage medium.
- Temporary (scratch) files generated by the system must be segregated from data and metadata of interest to users, auditors, and inspectors. These scratch files are intermediate products, used by the system to create user results and metadata. When stored in the same folder as user files, temporary files demand read, write, and delete rights to operate, which opens user files to unapproved changes and deletion. This major design flaw exists in many standalone systems on the market today.
- Audit trail entries are typically embedded in the individual data files;

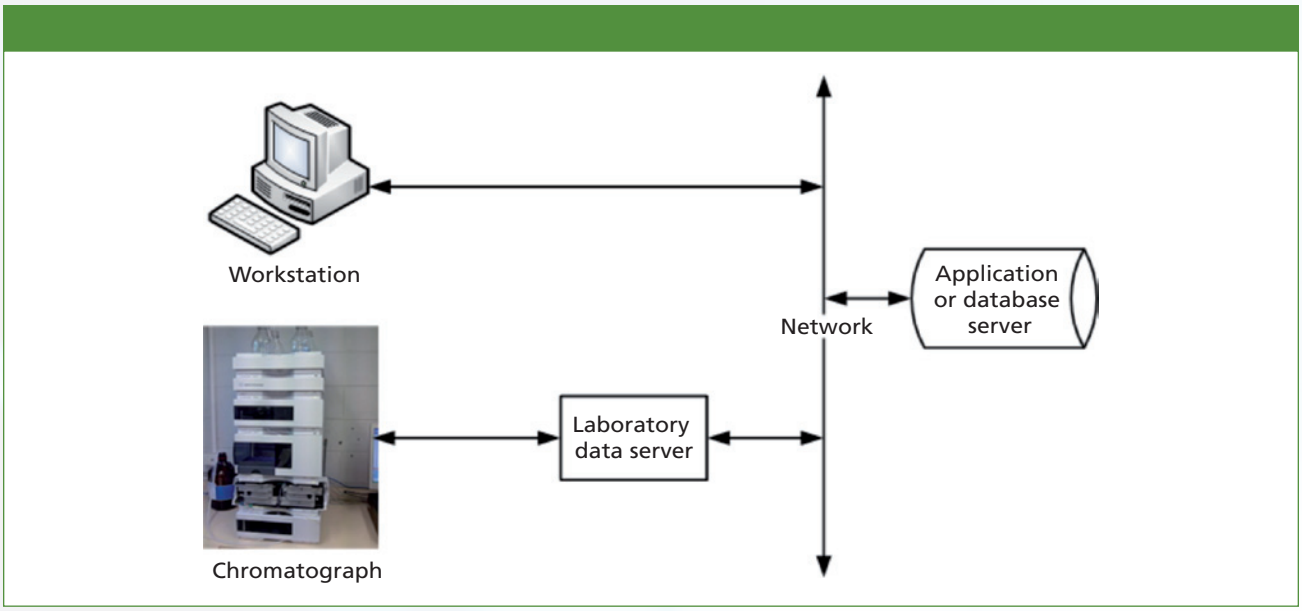

Figure 1: Overall CDS architecture diagram.

if a file is deleted the corresponding audit trail is deleted as well.

- Access to the operating system and the system clock must be restricted to authorized administration personnel. No normal users should have the capability to access these portions of the system.

All-in-all, a database is a much better way to go for the future CDS.

Independent IT Support

Independent IT support is essential to separate administration of the system from the normal chromatographic analysis functions of the software. This support ensures that analytical staff do not have access to change items such as turning the audit trail on or off or modify the date and time of the system. Therefore, the following functions need to be included under this section:

- Setup and management of the software application settings: The IT department should set up the configuration software settings that have been defined and documented by the laboratory and maintain them under a formal change control process. This management by the IT department ensures that laboratory staff cannot make changes to the configuration of the software directly.
- User account management: The definition of user types and the associated user privileges will be performed by the laboratory staff, but implemented and maintained by IT.
- Time and date settings: Networking the data system has the benefit of taking the date and time stamp setting out of laboratory control. Time and date settings are potential sources of tampering to affect the results.

IT staff should be the only people with access to the network clock, which is synchronized with a trusted time source such as a Network Time Protocol (NTP) server or a government agency such as the US Naval Observatory or Greenwich Mean Time (GMT or UTC).

- Data backup and recovery: If data backup is left to the laboratory the possibility arises that the work is not actioned or not done correctly. Backup problems were found at Ohm Laboratories (6) where the backup was not performed or staff may lose data as the Food and Drug Administration (FDA) found at Cambrex Profarmaco (7). For IT departments, one of the key tasks is backup and recovery of data and this process can and should be automated and carried out by IT, independently of the originating analytical laboratory.

Interfaces to Instruments and Systems

As we mentioned in part I of this series (1), a CDS should not exist in isolation. A CDS needs the capability to be interfaced with some analytical instruments as well as other informatics applications for business reasons. Essentially the whole purpose of interfacing is to eliminate manual data entry as much as possible, or reduce it substantially and replace it by seamless data transfers from where the data were originally acquired. For example, the CDS should be able to electronically accept sample identities, electronically match CDS results to them, and forward sample and results to a system, such as a laboratory information management system (LIMS), for batch evaluation.

As an example, the main CDS workflow can be made electronic, but there is still a large amount of manual data that must be input into the application such as sample weights, purities, dilution factors, and so on. To avoid the need to record weights from the balance, manually enter them into the CDS, and check them (these are critical data under clause 6 of EU GMP Annex 11 [4]), analytical balances should be interfaced to an informatics application. This informatics application can either be the CDS itself or another system, such as an electronic laboratory notebook (ELN) or LIMS, from which the weights can be transferred to the correct sequence file using a validated routine.

Following the analysis, the electronically signed CDS results need to be transferred for comparison with the specification either to a LIMS or an ELN, thus avoiding the need for transcription checking. In all of these interfaces, audit trail coverage of the transfer is essential to record the acquisition of data from one system in the audit trail.

Another consideration is buffering of data, to prevent loss if the CDS is temporarily down while an assay is running. Interfacing permits the use of buffers to prevent data loss.

Open Data File Formats

In the 1990s there were attempts at data file standardization for chromatography data systems, so the network common data format (NetCDF) file format was adopted for them. However, this approach is inadequate because it only covers the data file itself and not the metadata that surround it, such as sequence, instrument control, data acquisition, and processing files that put the data file in context. Because the regulators are demanding longer retention periods, such as for the time that a marketing authorization is in force (8), then a move to a file format that permits long term access to the data is imperative.

The American Society for Testing and Material's (ASTM) Analytical Markup Language (AnIML) is the main approach for a solution to the archiving issue that has been developed by the ASTM subcommittee E13.15 (9). The solution is text based rather than a binary file format that includes all contextual metadata.

Summary

In this part of our discussion on the future requirements for a CDS for regulated environments, we have discussed how any system must be networked with a database to ensure that any data generated have the integrity from acquisition to reporting. Furthermore, key support functions such as software configuration, user account management, and backup must be controlled by an independent IT group.

Interfaces to other instruments and systems are essential to ensure electronic acquisition and transfer of data while eliminating manual entry and manual transcription checks.

Finally, we need nonproprietary data file formats typically based on the new ASTM AniML standard to provide a mechanism for longer term archiving.

Acknowledgments

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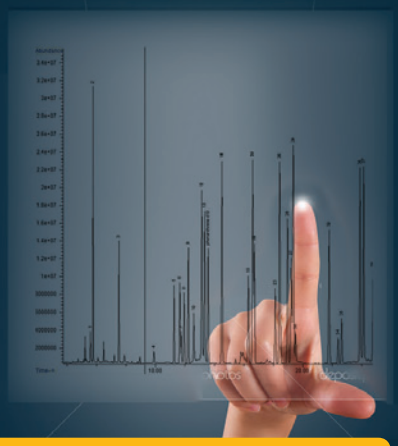
Achieve More with the Right Chromatography Data System



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EVENT OVERVIEW:

Today's chromatography laboratory is faced with a growing number of business challenges: reducing time-to-results, meeting increasing requirements for regulatory compliance, maximizing productivity through optimal instrument asset utilization, while reducing operational costs. Having the right chromatography data system (CDS) software is critical to addressing these challenges. Of course, replacing an existing CDS is an important decision and requires lab decision-makers to take a number of key factors into account. What should be considered when selecting a CDS? In this webinar, we will share with you what is involved in making the change and how you can prepare for it. Additionally, you'll learn how you can increase productivity in your lab by using the significantly improved data analysis and reporting features that the right CDS has to offer. Key questions that indicate that you should tune into this web seminar include:

- Is your software running on an out-of-support operating system?
- Do you use programs like Microsoft Excel for calculations and reporting?
- Are you unable to take advantage of the latest instrumentation due to lack of software support?

Who Should Attend:

- **Decision Makers:** Analytical Services, Method Development, Production, QA/QC, R&D, Lab Manager, Manager/Dept. Head, Scientist/ Chemist, Technical Decision Maker
- **This information is valuable for all companies planning to upgrade the software in their labs**

Key Learning Objectives:

- Learn of the many advantages a move to the right CDS can offer
- How you can reduce complexity and improve efficiency in your lab
- How to boost lab productivity by simplifying operations

Presenters

Thomas Schmidt
OpenLAB CDS
Product Manager

Michael Spezia
Senior Professional
Services Engineer

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For questions, contact Kristen Moore at kmoore@advanstar.com

THE IDEAL CHROMATOGRAPHY DATA SYSTEM FOR A REGULATED LABORATORY, PART III: ESSENTIAL CHROMATOGRAPHIC FUNCTIONS FOR ELECTRONIC WAYS OF WORKING

R.D. McDowall and Chris Burgess

In the first two parts of this series we looked at where and how a chromatography data system (CDS) fits into a regulated laboratory and the overall requirements for the architecture of a future system. In this part, we focus on new electronic ways of working for chromatographic analysis.

In the first article in this series (1), we looked at the role of the laboratory and discussed the concept of the analytical factory together with the controllable and uncontrolled factors influencing the analytical process. In addition, we looked at the requirements for ensuring data integrity throughout the analytical process. We began the second installment (2) by defining the overall system architecture for a compliant chromatography data system (CDS) in a regulated laboratory in more detail. Here we describe the electronic processes and workflows that the future CDS should be capable of to improve efficiency and effectiveness.

Where Are We Now?

Basic chromatography functions that are already present include instrument control, data acquisition, integration, calculations, and reporting electronic signatures. Indeed there have been publications on how to implement and validate electronic ways of working including electronic signatures using a CDS (3,4) that are now 10 years old. However, when you look in detail at the workflow that has been implemented it focuses on chromatographic analysis only. Furthermore, control of an analytical procedure is either on (no changes permitted) or off (any changes permitted). There needs to be a more rational approach to changes based on the validation of the procedure.

Where Do We Need and Want to Go?

There are still areas where there are significant manual inputs to the chromatographic process—for example,

Table I: New chromatographic data system functions and their scope

New CDS Functions	Scope of the Function
Procedure development	• Experimental design software: definition of design space • New functions for experimental design and defining analytical control strategy • Robustness experiments to determine the design space and refine the analytical control strategy • Generating summaries and tables of work performed for a method development report
Analytical procedure validation	• Link to procedure development results and analytical control strategy • Procedure performance qualification (PPQ) for CDS: user defined experiments for qualifying an analytical procedure (this module could also be used for technology transfer between laboratories) • Generating summaries and tables of work performed for a PPQ validation report
Trending analytical data	• Link to method validation or transfer results and the analytical control strategy • System suitability tests (SSTs) conducted throughout the run and evaluating the data stream • In-process controls for controlling quality of the analytical run • Trending data between runs: key SST results, analytical results • Operational use of a procedure: trending data—identifying special cause variation of a procedure (identifying shift and drift) • User-defined action and warning limits • Process capability determination
Electronic working—new features	• Notification of work to do when you log in such as supervisor – data to review or work to do if an analyst • Column logs—automatic data collection via radio frequency identity (RFID) tags—tamper evident. Available now for single CDS and same supplier but need universal standards such as any supplier's column with any vendor's CDS • Instrument maintenance and use log—scheduling of preventative maintenance and qualification activities, automatic data collection with results and documented review by laboratory staff
Laboratory investigation module	• Laboratory investigations for OOS, OOE, and OOT—configurable function for this. The CDS has acquired information from the run about the solutions and standards used, methods, integration, SST, manual entry of data for the run. • Can provide a step by step prompt for the first phase laboratory investigation but must be user defined to fit with a laboratory's SOPs

sample information, sample weights, instrument log books, and column log books require manual input. In addition, method development and validation are typically outside the scope of an electronic process. However, we also want to go further and examine what the current regulations require of analytical laboratories from the perspective of trends in regulations (5,6).

Table I lists five new functions that we consider essential to a next-generation CDS working in a regulated laboratory. These are intended to go in parallel with the current functions that enable the main chromatographic process to work electronically. In addition we need to consider the development of an analytical procedure and its validation and operational use. We discuss each of those areas in more detail below.

Requirement 1: Method Development Function

The United States Pharmacopeia (USP) stimulus paper advocates defining an analytical target profile (ATP) (7), as we discussed in part I of this series (1), and this profile is then broken down into the overall analytical procedure including the sampling plan. However, focusing on the chromatographic portion of the process, the key to procedure development is an understanding of how key variables in the analytical procedure impact on the quality of the separation and robustness of the method (defining the analytical control strategy). Therefore, the CDS needs to automate the design, conduct, and evaluation of separation experiments. Some existing chromatography data systems have been integrated with experimental design software with the ability to control chromatographs so that results of individual experiments can be fed back into the design software for evaluation. Although chromatography data systems have the ability to perform some of these functions, the new approach proposed by the USP needs to be incorporated into CDS software. This integration is essential—defining the analytical control strategy is important because it is used throughout a procedure's operational life. Changes can be made within the analytical control strategy to revalidate the method, and for this reason it must be available within the CDS.

The CDS should be capable of abstracting the work performed in developing the procedure for inclusion in a method validation report.

Requirement 2: Analytical Procedure Validation

Linking the method development work with *procedure performance qualification* (PPQ), the new USP term for method validation, of the analytical procedure is the next logical step with our new CDS. PPQ is essentially what we currently call validation. PPQ experiments, consistent with the ATP and within the analytical control strategy, can be defined by users as well as the acceptance criteria for each parameter and carried out by the system. On completion of the work, the calculated results can be interpreted by the CDS against the acceptance criteria and generate the secure result tables created for inclusion in the procedure performance verification (method validation) report automatically. This will typically be prepared outside of the data system.

By implication, the software should also be suitable for defining procedure performance verification (PPV) protocols and reports (see **Figure 2** in part I [1]). This process will use the same software functions as above.

Requirement 3: Trending Analytical Data

The USP stimulus paper on control of methods during routine use has applied the following documented strategies: ICH Q10 (8), *European Union Good Manufacturing Practice* (EU GMP) Chapter 1.10(vii) (5), and the new EU GMP Chapter clauses 6.7(iv), 6.9, 6.16, 6.32, and 6.35 (6) for trending of quality control (QC) data. Therefore, as a minimum, a CDS needs to have the statistical functions to trend data such as the individual and mean results along with the key system suitability test (SST) parameters defined by users. Usually the limits will be based on the validation parameters of each analytical procedure. These data can be presented, for example, as a Shewhart plot with action and warning limits with the aim of identifying trends before an analytical procedure produces an out-of-specification (OOS) result. The CDS should then allow a user to look at instrument or column use in the method to see if there are any issues around a specific instrument or column. Any issues found may require an interface from the CDS to another informatics package for deviation management, risk assessment, and corrective and presentative action plans (CAPA) should be available.

Additionally, data trending is required for product quality reviews (5), where all batches of a specified product would be reviewed within the CDS with the output of secure tables for the overall reports of product quality.

Requirement 4: Additional Functions for Electronic Workflows

Currently, electronic workflows are poorly supported in current CDS applications. By this statement we mean that work packages are not allocated to teams of analysts to perform the work and peers or supervisors to review the data when the analysis is completed. The allocation of work and informing a user when a dataset is ready for review typically occurs outside of the data system. What is required is when you log in to the CDS either as an analyst or a supervisor there is a notification of the work to be performed by a team. This function needs to integrate with other informatics applications such as a laboratory information management system (LIMS) or an electronic laboratory notebook (ELN) for this to occur.

As required by the GMP regulations, there are instrument and column logs to complete when conducting an analysis. Typically, this is performed manually even if the main CDS workflow is electronic. For instrument use this information is typically contained within the CDS. What is required is a function to list the chronological use of each instrument,

for example, instrument identity, date, analysis performed, analyst name (not identity), number of injections, and so on. In addition, there need to be functions in the CDS to record the following instrument data:

- Usage (such as the amount of mobile phase pumped, lamp hours, number of injections) of each instrument controlled as opposed to merely acquiring data from the detector
- Performance monitoring, dependent on the configuration of each instrument, such as mobile-phase pressure over time or lamp energy

These two sets of data should be used by the CDS to help manage predictive maintenance. The data can be used to establish and manage maintenance patterns based upon instrument usage and performance patterns. This maintenance would be risk-based and scheduled on actual data rather than estimated.

As mentioned next in requirement number 5 and in Table I, there needs to be a laboratory investigation module. The data from the instrument, column usage, and performance data can be fed into the investigation of an OOS, out of expectation (OOE), or out of trend (OOT) for use by the supervisor and analyst conducting the initial phases of the investigation. When necessary there could be diagnostic testing of the chromatograph conducted via the CDS. The overall aim is to understand the potential contribution of the instrument to the OOS result. These functions should be configurable in the CDS to allow a degree of focus in any investigation. Where possible, specific instrument events during an analytical run can be reviewed during the investigation. Additionally, where there is an instrument failure or breakdown or qualification failure, the CDS should support the impact assessment process, in which the potential impact of the instrument failure on the analytical results is evaluated and documented.

If there is sufficient IT security, the CDS could be connected to a service provider for remote diagnostics and service support. This function needs to be controlled in such a way that the service provider is allowed access only when the regulated laboratory requests help.

There needs to be a search function across and within instruments as well as the ability to access data generated in runs, especially if the search function is combined with the trending functions of the new CDS. In addition, this feature could identify potential problem instruments or justification for a new instrument as the existing ones are overloaded. One further step could be to expand the log to include maintenance either by a supplier, service agent, or laboratory staff, enabling all information to be in a single location that is reviewable and searchable.

Column logs are maintained manually in a large number of laboratories despite advances that could make them redundant. CDS suppliers who

also sell columns have radio-frequency identification (RFID) tags that can be read by their software to identify the column number, packing, dimensions, and so on. However, what we want is for this identification to be extended to any column from any manufacturer so that a laboratory can use the most appropriate column for the analytical procedure. Here, the CDS can provide the column log information using similar functions as the instrument usage log.

Note, that the instrument use, maintenance, and column logs need to document that they have been reviewed by a second person. This function would also need to have a reminder function in case of memory lapses by reviewers.

Requirement 5: Laboratory Investigation Module

Finally, there should be the user-definable functions for the first stage of a laboratory investigation for OOS results that should be linked with the trending functions for analytical data and SSTs described earlier in this article. Part of the function would be for users to set, for each analytical procedure, the acceptance criteria for individual injection results as well as the reportable value of the sample as described in the Food and Drug Administration's (FDA's) guidance on the subject (9). The first stage investigation could be set up as a series of questions to be completed by the analyst and supervisor as they review the analytical data—such as the solutions and standards used, sample weights, test methods, integration, SST, manual entry of data for the run, and so on. If there was an assignable cause, the supervisor should review and approve the investigation. If not the investigation would be transferred to a corporate system for further work.

Summary

In this article we looked at defining new functions for the future CDS to automate the development, qualification and procedure development, procedure performance qualification, and procedure performance verification. In addition, new features for electronic working, electronic instrument and column use logs that are automatically completed by the application, trending functions to be compliant with the new requirements of EU GMP Chapter 6, and the linkage with a user-defined first stage laboratory investigation module were discussed.

Acknowledgments

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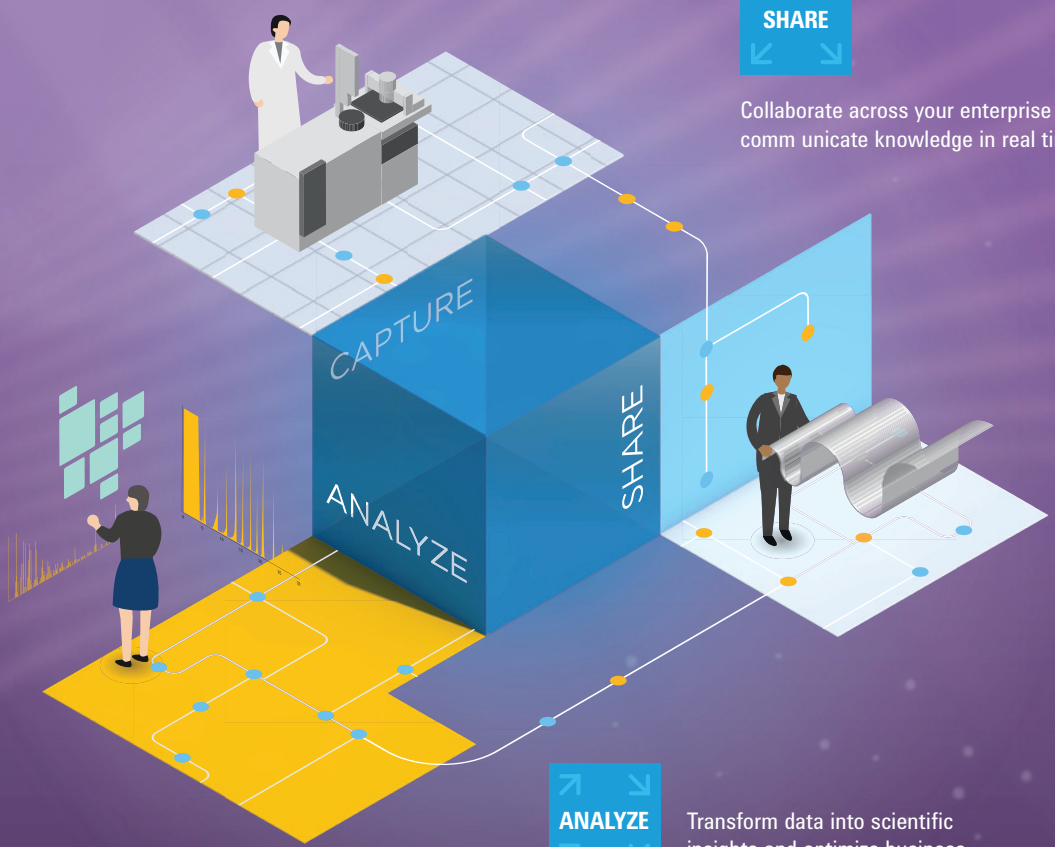

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THE IDEAL CHROMATOGRAPHY DATA SYSTEM FOR A REGULATED LABORATORY, PART IV: ENSURING REGULATORY COMPLIANCE

R.D. McDowall and Chris Burgess

The first three articles in this series discussed where and how a chromatography data system (CDS) fits into a regulated laboratory, the overall requirements for the architecture of a future system, and additional items to enable effective electronic ways of working. The final part of this series looks at regulatory compliance of a future system and provides a summary of the 15 recommendations made in this series.

In the first article in this series (1) we looked at the role of the laboratory and discussed the concept of the analytical factory together with the controllable and uncontrolled factors influencing the analytical process. In addition, we looked at the requirements for ensuring data integrity throughout the analytical process. We began the second installment (2) by defining the overall system architecture for a compliant chromatography data system (CDS) in a regulated laboratory in more detail. In the third part (3), we described the new functions required to create fully electronic processes and workflows that should be incorporated into a future CDS to improve efficiency and effectiveness. In this, the last part of the series, we look at regulatory compliance features that must be present in any CDS for trustworthy and reliable electronic records and electronic signatures, thereby ensuring data integrity. To complete this series, we summarize all 15 recommendations made, to describe what the future CDS should look like.

Where Are We Now?

Although chromatography data systems operating in regulated laboratories have basic controls for regulatory compliance there is still a lot that is driven by paper, such as system configuration and instrument qualification. The latter is particularly the case, as suppliers use their service personnel to deliver qualification services, but provide reams of paper for them to fill in for their customers to review. Mistakes, especially by the service personnel, abound as the authors have

found when reviewing such documents when advising clients. Moving to an electronic process will eliminate many of these problems and allow fast, electronic review by the laboratory staff. Other areas for compliance improvement include increased data integrity features, improving audit trail content and review, as well as handling unattended working.

Where Do We Want to Be?

From the regulatory perspective a CDS operating in a GXP (good manufacturing, laboratory, or clinical practice) regulated environment should be capable of the following functions:

- documenting the software and instrument configurations of the system,
- automated instrument qualification,
- securing metadata and ensuring data integrity,
- enhanced audit trail functionality to meet current regulatory requirements, and
- compliance control for unattended working.

Each of these areas is discussed in turn in the sections that follow.

Requirement 1: Documenting Configuration Settings

A CDS consists of configurable software that is good automated manufacturing practice (GAMP) Software Category 4 (4), and when used in a regulated laboratory, the system must be validated. One area that needs to be documented is the configuration of the system. This consists of two parts: the first is the software and the second is the overall instrument configuration. Typically, the software settings that need to be configured to meet the business and regulatory needs of a laboratory or organization are definition of user types and the corresponding access privileges, password length and complexity, use of electronic signatures, and electronic records protection. Currently few, if any, chromatography data systems allow a user to document these settings without resorting to a paper-based process. Because the data are contained within the system, would it not make sense to have a function that performed this automatically? Incorporating a search function could allow the system to document the changes over time.

Similarly, the configuration of data servers and chromatographs attached to the CDS should also be available to be documented via the software rather than requiring documentation outside of the system as paper records.

Requirement 2: Automated Instrument Qualification

As noted above, execution of operational qualification protocols is traditionally performed manually with the attendant issues of incomplete signing and dating of all appropriate sections. In addition, the documentation review by the laboratory staff may take time and the engineer may be off-site before errors are found. What we envisage is that the

operational qualification protocol for each instrument together with the predefined or user-defined acceptance criteria will be available in the CDS and each protocol will be preapproved by electronic signature before execution.

A service engineer or third-party agent will have limited access to the data system to execute the operational qualification (OQ), gather results electronically, where necessary entering data manually, and document and resolve any discrepancies. The CDS must identify the individual carrying out the work via the log-on credentials. Unless the OQ is reviewed and approved by laboratory staff the instrument cannot be used for regulated work; thus there is a driver to ensure timely review and approval of the data and results versus acceptance criteria.

Based on a user-defined period, the time for the next OQ will be set in the CDS and reminders will be sent before expiry to the instrument owner or the person responsible for instrument qualification. If required, a user-defined grace period can be specified in the system after which the instrument would become unavailable for use if an OQ had not been performed.

The automated instrument qualification procedure is defined by the vendor, but the scientific soundness is attested to by the user. Therefore the procedures and qualification standards employed must be defendable both in terms of good science and traceability to a national or international standard. Currently some vendor practices do not meet these requirements in the second respect. Hence, it would be ideal if the vendor provided the automated tools, but allowed the user to configure the reference materials used to determine criteria such as wavelength accuracy, response linearity, and resolution. However, any change in the acceptance criteria would have to be scientifically sound and justified within the system.

Requirement 3: Securing Metadata for Ensuring Data Integrity

One of the reasons for writing this series is the issue of data integrity in falsification cases found during European Union (EU) and Food and Drug Administration (FDA) inspections (5). The data files generated by any CDS are checksummed to detect and prevent tampering with them. However, examination of data falsification warning letters shows that the main thrust of falsification attempts are manual changes of factors, purities, sample weights, and integration parameters. Therefore, of necessity, data integrity and the associated audit trail entries must cover any changes made to the contextual metadata generated during any chromatographic analysis. This is vitally important as a value of 7.5 is useless without the context of the measurement with respect to units, composition, analysts, instrument, column, lot number, analytical method, and so forth. These contextual metadata are also essential for long-term retention and archiving.

Therefore, in the new-generation CDS it is essential to ensure that only changes to sequence, instrument control, data acquisition, and processing files can only be made by authorized users. This is particularly important for integration parameters. The overall requirements in the data integrity life cycle can be seen in Figure 5, which we presented and discussed in part I of this article series (1).

Requirement 4: Improved Audit Trail Review

Although all CDS applications used in regulated laboratories have audit trails, they are not adequate to meet today's regulations in an effective way. The key requirement is for audit trail entries to be reviewed by a second person (6–9). According to *Annex 11* (6), data entries that have been modified or deleted need to be tracked. This applies to both the chromatography data files, for example, manual intervention in the integration of peaks as well as monitoring changes to the associated metadata used by the run such as sequence file and instrument, acquisition and processing methods, and so forth. The design of the audit trails needs to be smarter as well—it is not the sole purpose in a reviewer's life to trawl through hundreds of audit trail entries as a chromatographic version of Indiana Jones. CDS suppliers need to define an audit trail dashboard that covers all data and metadata in a run and present this as a traffic light. Traffic lights would work on the principles that green shows where no operator changes or deletions have been made to data, yellow shows where there have been modifications, and red show any data deletions (if allowed by access privileges). This would allow a second person to review by exception only those entries in yellow or red. An alternative approach could be a function that automatically identified modifications or deletions then notified a supervisor or administrator at the start of the second-person review.

The new function also needs to record that the audit trail has been reviewed by a second individual and no action was needed (all green entries) or modifications have been reviewed and that they are acceptable and within the laboratory's procedures. Also, the ability to set review frequencies on each audit trail (policies, if you prefer) would be a good feature as the function could generate a reminder when a review interval is reached.

For the future CDS, we also need a function that tracks the export of data to other systems via audit trail entries. Many stand-alone systems permit a person to run an assay several times, then pick their favorite run and forward to a laboratory information management system (LIMS). These systems do not track the forwarded runs, so there is no way to quickly identify raw data that is still not included in some test record (at least justified in the CDS as to the rationale for the selection of the data forwarded). Agreeing on injection naming

conventions—linked to CDS functionality would help here, along with a simple secure injection sequence log, where appropriate justification is provided as to why each injection in the sequence is performed. Although this may seem draconian, it could make instances of incomplete data, or where the wrong naming convention has been applied, visible in a second-person review.

After all these audit trail functions have been validated, a laboratory can ensure that many second-person reviews can be made speedier and much more efficient.

Requirement 5: Compliance Control in Unattended Analysis

One of the issues with current networked chromatography data systems is that if a run is started and a user goes home how can any changes be made to the run by an authorized user? The assumption made by most, if not all, chromatography data systems is that the user logged in at the start of the run is the same one that makes any subsequent changes, which may not be the case. There needs to be a function, linked to the audit trail, that if an authorized user needs to access a run when the initiating user is not available they can log on and make changes that are attributed to the new user's identity rather than the originating user.

Regulatory Enhancement Summary

In this article, we have looked at five areas that we believe will bring better regulatory compliance when using a CDS in a GXP laboratory. The ability to document configuration settings quickly and effectively will be useful in initial validation of a CDS, audits, and inspections as well as periodic reviews. Automated electronic qualification of instruments should be the norm rather than slow and error prone execution of paper protocols. Securing metadata in combination with effective audit trails are key compliance features. These additions, along with a documented review of key audit trail entries by exception during the second-person review, are essential productivity and compliance enhancements of any CDS while maintaining compliance with the regulations. Finally, the ability to secure a system during a long analytical run but also have another user access the system and make authorized adjustments under their own name is a key compliance requirement that is not addressed currently.

Bringing It All Together

In this series of articles, we presented 15 areas for improving a CDS for operating in a regulated environment and in this final section we collate and present them in two diagrams.

Figure 1 presents the high-level view of a future networked CDS system where data are stored in a database. The system is interfaced in the laboratory to the chromatographs, but also to an analytical balance to

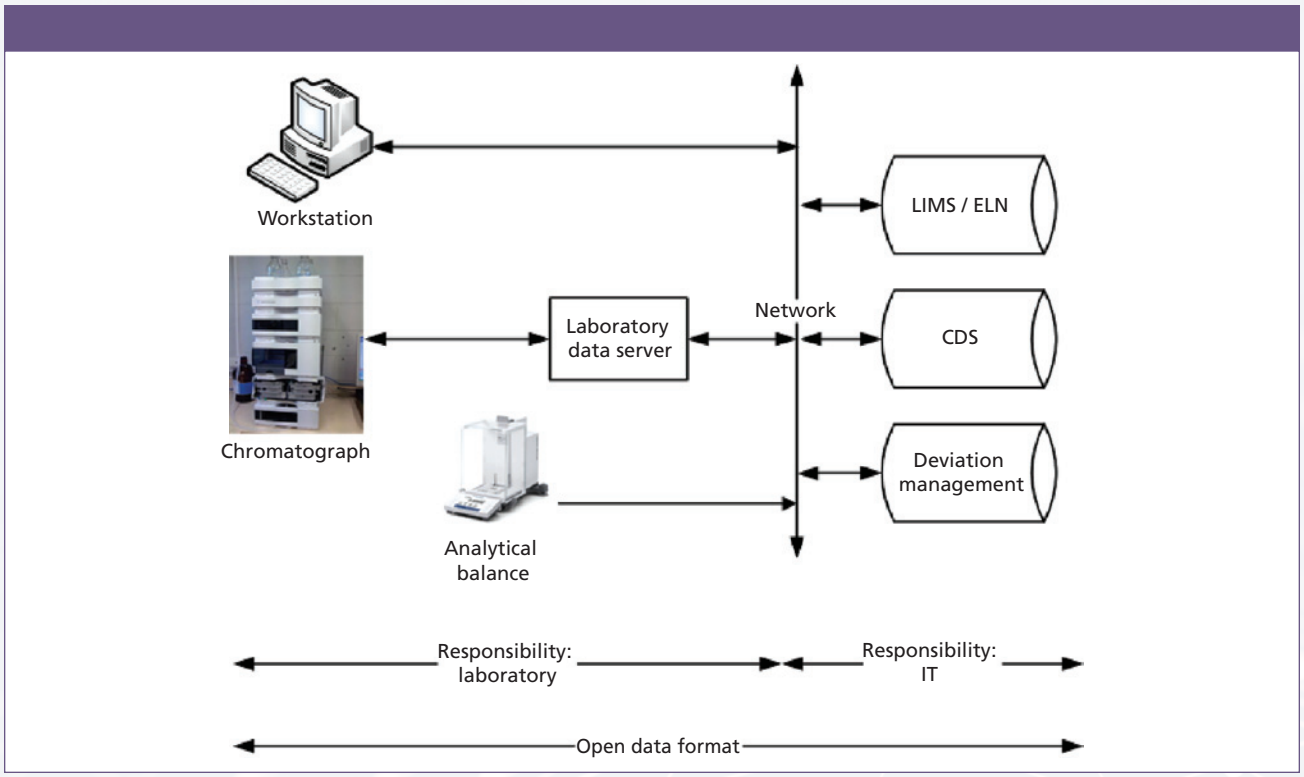

Figure 1: Overall CDS system architecture, informatics connectivity, and responsibilities.

avoid manual transcription of sample weights. Acquired data and metadata are stored in open file formats to allow long-term record retention. The CDS is also interfaced with other informatics applications such as a LIMS or electronic laboratory notebook (ELN) and a deviation management application. Responsibilities for the system are also outlined in Figure 1, with the laboratory staff who are responsible for analytical aspects of the application and IT staff who are responsible for the configuration of the application, user account management, and backup. Data must be acquired, processed, and stored using open file formats for long term retention and interoperability.

The working of a future CDS in a regulated environment is shown in Figure 2. This figure is based on the overall process flow used in Figures 3 and 5 from part I of this series (1). Under this we have placed four threads: system setup, enhanced compliance, analytical procedures, and electronic working.

- System setup covering documentation of system configuration, electronic qualification protocols and their execution by the CDS, and open file formats for the data files and the contextual metadata
- Enhanced compliance features for a new system include compliance control for unattended operation of instruments, means of securing the

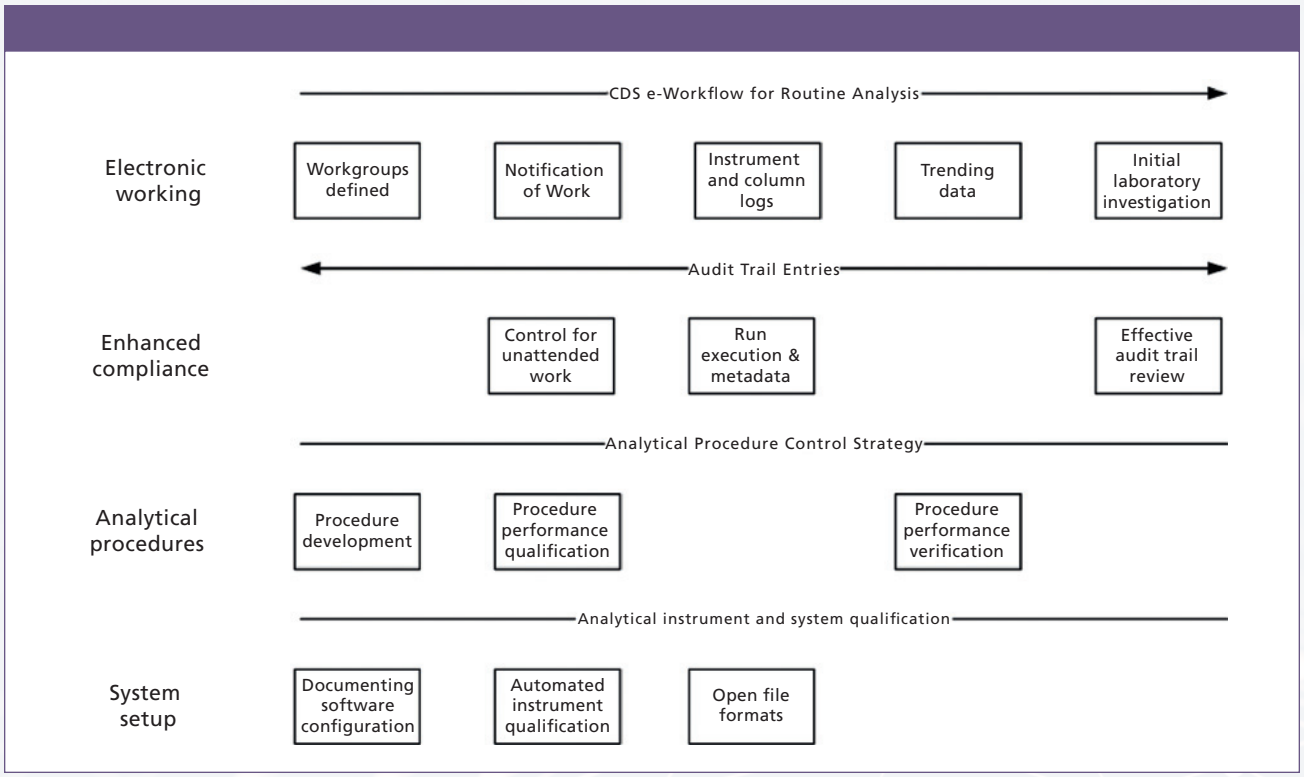

Figure 2: Additional functions and features for a future CDS in a regulated environment.

contextual metadata of an analysis, and effective audit trails to enhance data integrity and second-person data review by exception.

- Analytical procedures covering the spectrum from procedure development, qualification (validation), and verification upon transfer to another laboratory.
- Electronic working including the set-up of workgroups with notification of work to be performed (either analysis or review of data), electronic instrument and column logs that are completed by the CDS rather than manually, trending of data within and between runs, and a user-defined module for performing the initial stages of a laboratory investigation

Although we show these features and functions as stand-alone items this would not be the case in practice. Take, for example, the development of a procedure and its associated procedure performance qualification, data generated during these stages would input into the trending module for the procedure. The analytical control strategy would define the extent of any change that would be allowed without the need to requalify the method, see the process flow in Figure 2 from part I (1). There are further linkages and interactions between other suggested enhancements shown above.

Summary

In this four-part series we have positioned a CDS or similar informatics solution in terms of a regulated environment. The business process that a CDS automates is envisioned as an analytical factory with controlled and uncontrolled factors. The enhancements suggested in this series are intended to ensure that a future CDS can work electronically in an efficient and effective way to generate data with its integrity ensured. Furthermore, the data and metadata are generated in a format that ensures that they can be retained throughout the record retention period.

The 15 proposed areas for enhancement are the major ones envisaged for a future CDS in the short to medium timeframe. They are not intended to be exhaustive or complete. However, these functions will not appear magically in the next release of your CDS system. To be fair to the suppliers of these applications, users need to demand them as these companies are market-led. If you think that these features will be of use in the future, what are you going to do about it?

Acknowledgments

The authors would like to thank Lorrie Scheussler, Heather Longden, Mark Newton, and Paul Smith for comments and suggestions made during the writing of this series of papers.

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