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Delivering Data Security, Integrity, and Credibility: Your Reference Resource for Using a Modern Software System to Ensure Compliance

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The Ideal Chromatography Data System for a Regulated Laboratory, Part IV: Assuring Regulatory Compliance
Chris Burgess and R.D. McDowall

Flexible CDS Software Brings Big Gains to Analytical Laboratory
Interview with Alison Lynch and Adam Neaves

Ensuring Data Integrity and Compliance with a Modern Chromatography Data System
Interview with Shaun Quinn

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INTRODUCTION

A chromatography data system is a critical component of a laboratory's data management system. From research to quality testing, a modern CDS not only helps laboratories ensure regulatory compliance, but also helps analysts to be more productive. *Delivering Data Security, Integrity, and Credibility: Your Reference Resource for Using a Modern Software System to Ensure Compliance* offers laboratories insight into how a CDS can streamline workflows, minimize errors, provide easy tracking and defence of data, and increase a laboratory's efficiency.

First, hear from R.D. McDowall, Director of R.D. McDowall Ltd., and Chris Burgess, Managing Director of Burgess Analytical Consultancy Ltd., about how a chromatography data system (CDS) fits into a regulated laboratory. McDowall and Burgess also propose 15 areas for enhancing a CDS in the future.

Next, Alison Lynch, the Nicotine Containing Products (NCP) Services Manager at Broughton Laboratories, and Adam Neaves, a Quality and Compliance Technical Specialist for Broughton's pharmaceutical clients, describe how implementing a modern CDS is helping their laboratory meet the needs of its growing clientele with rapid analyses, regulatory compliance, and expanded services.

Readers will also learn from Shaun Quinn, Marketing Manager of Compliance, Chromatography Software, focusing on eRecord regulations and compliance at Thermo Fisher Scientific, about challenges that laboratories face in terms of maintaining data integrity and how a modern CDS can help.

The Ideal Chromatography Data System for a Regulated Laboratory, Part IV: Assuring Regulatory Compliance

Chris Burgess and R.D. McDowall

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.

"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."

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.

"The ability to document configuration settings quickly and effectively will be useful in initial validation of a CDS, audits, and inspections."

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

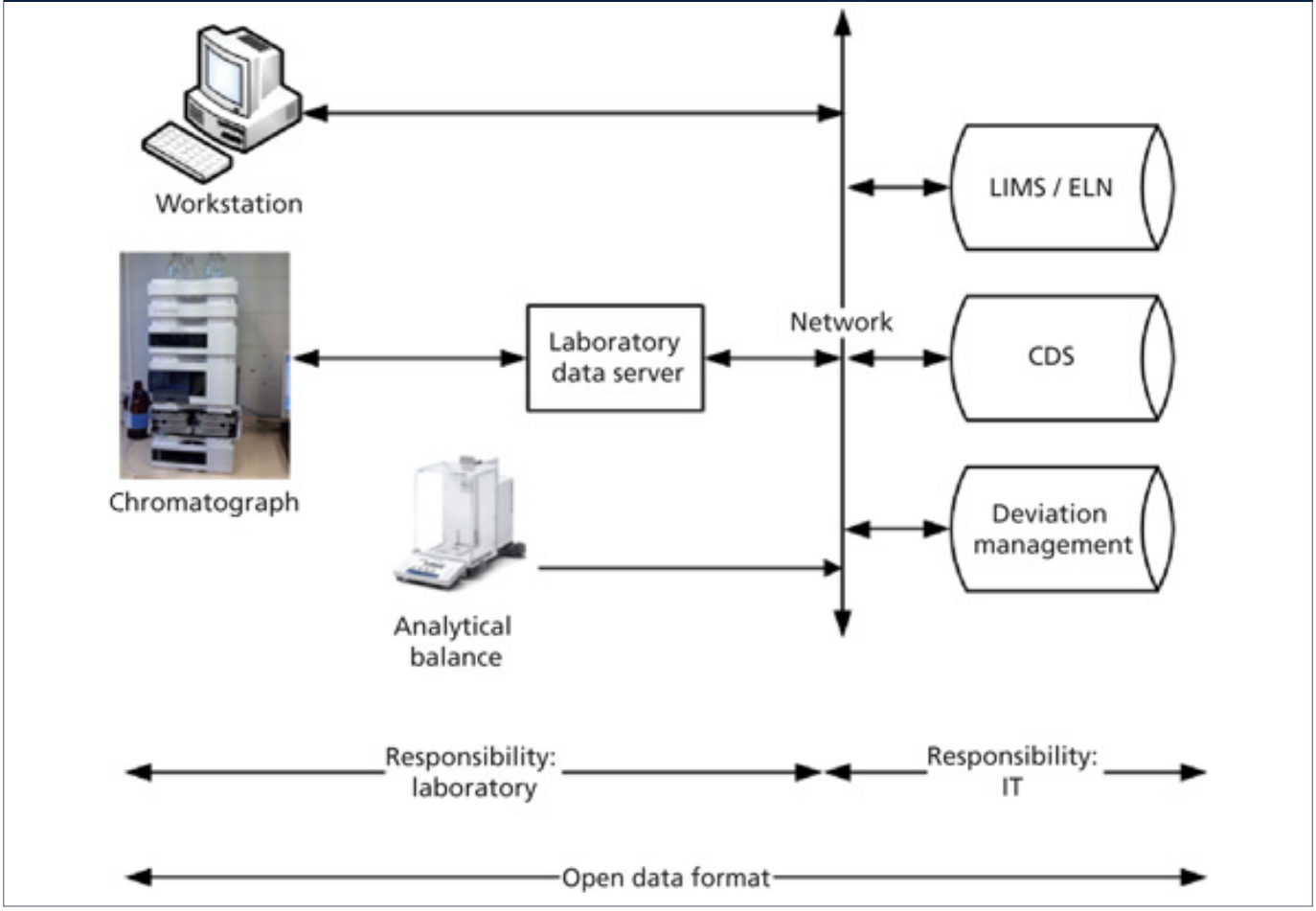
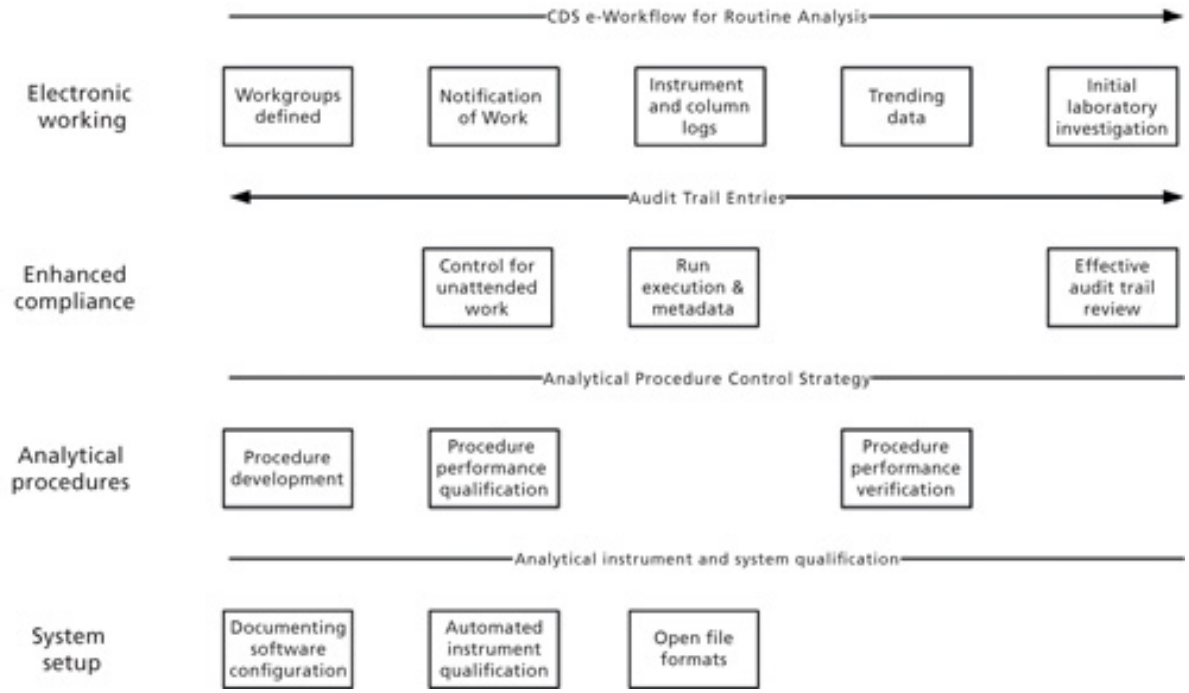


Figure 1 presents the high-level view of a future networked CDS system where data are stored in a database. The system is interfaced in the laboratory to the chromatographs, but also to an analytical balance to avoid manual transcription of sample weights. Acquired data and metadata are stored in open 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.

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



- 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 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 previously.

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

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Flexible CDS Software Brings Big Gains to Analytical Laboratory

Interview with Alison Lynch and Adam Neaves

Analytical laboratories are increasingly tasked with boosting productivity while ensuring the accuracy and reproducibility needed to deliver safe and effective products to market. Laboratories working in growing segments such as nicotine-containing products or highly regulated markets like the pharmaceutical industry have additional layers of complexity that must be considered and addressed. What tools are available to meet the needs of these testing labs?

Investing in a modern chromatography data system (CDS) with flexible software may pay dividends, according to Alison Lynch, the Nicotine Containing Products (NCP) Services Manager at Broughton Laboratories, and Adam Neaves, a Quality and Compliance Technical Specialist for Broughton's pharmaceutical clients. The laboratory recently expanded its capabilities while streamlining workflows and meeting compliance requirements by capitalizing on the flexibility of the Thermo Scientific™ Chromeleon™ 7.2 CDS software. Here, Lynch and Neaves describe how this system ensured the laboratory would continue to meet the needs of its growing clientele with accurate and rapid analyses, regulatory compliance, and expanded testing services.

Advantages of a Flexible CDS

When adding analytical services for nicotine-containing products—such as market-first testing for electronic nicotine delivery systems (ENDS)—to its existing portfolio of pharmaceutical, veterinary, and medical device testing services, Broughton Laboratories needed a single CDS and easy-to-use software that could manage all of its measurement, reporting, and compliance needs.

Compatibility. Speed, reliability, and flexibility were key requirements for the CDS, as was the software's compatibility with diverse analytical instruments. Multi-compound samples in the ENDS market are often mixtures of propylene glycol, glycerol, nicotine, and complex

flavor mixes. Many common flavorings can contain between 10 and 50 individual chemicals, which can often complicate the analysis by introducing chromatographic interference. Initially, analyses supporting the ENDS market used high-performance liquid chromatography (HPLC–UV) and gas chromatography with flame ionization detector (GC–FID). Three years ago, Broughton Laboratories began using mass spectrometry (MS) detection with the Thermo Scientific™ Endura™ Triple Quadrupole Mass Spectrometer to overcome interference issues and to shorten run times from 25 minutes with HPLC–UV to 5 minutes with LC–MS/MS. The ability to run faster analyses not only avoided the problem of limited sample stability, but also helped to quickly validate optimized methods for formulations, which Lynch says is critical "because of the speed that products are developed and changed in the e-cigarette world."

While the selectivity of MS/MS systems allowed Broughton Laboratories to provide a more accurate, confident representation of product to customers, the addition of mass spectrometers to the lab's chromatography systems could have complicated their analyses and reporting. Lynch and Neaves found instead, however, that the compatibility of Chromeleon CDS with hundreds of different instrument modules from numerous vendors allowed the laboratory to use one intuitive user interface for all its analyses.

This feature is important. Typically, instruments come with a CDS from the manufacturer, says Neaves, which creates difficulties from having several different data systems generating data with slightly different criteria, and different database systems underneath the CDS. That can lead to additional complexity and inconvenience when comparing data between different systems. Thus, it was important to Broughton Laboratories that the Chromeleon CDS was capable of managing a wide variety of instrumentation in one system.

"Being able to use one CDS to cover everything has been brilliant," adds Lynch.

Neaves agrees, stating, "From the single data system, we gain comparison capability, a single storage system, and a standardized approach. It also reduces training timing and re-validation."

Data integrity. Taking on ENDS work introduced another challenge for Broughton Laboratories: having to abide by different regulatory requirements for a new market. For the pharmaceutical side of its business, Broughton Laboratories needed a CDS that would support GMP compliance and maintain data security. The system would also need to be flexible enough to help the lab meet ISO and GLP requirements to support analysis for the ENDS market. Neaves says while there is some overlap between the requirements, the differences can affect key system configurations.

For instance, in a GLP environment, labs have the additional requirement of data archiving and the archivists' capabilities, which can create challenges within the user management system. To help address this issue, Chromeleon CDS has over 160 different privileges and unlimited security levels and user roles to meet a laboratory's specific needs.

Neaves states, "Chromeleon software's centralization storage and back-up as well as its customizable user management system regarding the permissions and the role types you implement into your specific environment are key data integrity requirements."

Fast, accurate reporting. With a diverse client base, Broughton Laboratories has many different reporting requirements that are all managed through the company's CDS software. Chromeleon CDS allows custom variables for easy report generation. Multiple samples for several clients can all be included in one analytical run, which will then produce multiple outputs. The streamlined data processing and quantitation are performed within the single CDS with no need for external software.

"All our client needs are met in one processing event effectively. It's so flexible. We can do it all within Chromeleon CDS and really design it to meet our needs," Lynch states.

Customized reports for specific analyses lend efficiency to the workflow. Analysts generate the data, which can then be easily verified by a senior analyst and reviewed by a manager. Chromeleon software's reporting and verification process reduces the burden of data checking and provides an electronic data audit trail. The validation documentation and controls, such as audit trails, electronic signatures and data security, follow GMP requirements for data integrity. And the software is amenable to the requirements of different regulating bodies, as well as ISO and other quality standards. "We looked at Chromeleon CDS to help improve that process by reducing the burden of checking data and calculations through a manual system, which was essentially what we were using, and move toward an electronic data audit trail assessment of change, and assessment of the integrity of the data that we generated," Neaves says.

> **"All our client needs are met in one processing event effectively."**
> **—Alison Lynch, Broughton Laboratories**

All told, transitioning to using HPLC–MS analysis and implementing a flexible CDS have increased the speed of getting samples onto systems and reporting the results. With Chromeleon CDS and templating, systems are easily set up with sequences of samples for quick, efficient, accurate, and reproducible analysis.

The improvements Broughton Laboratories has seen with the CDS are significant. Says Neaves, "We've seen reductions of up to 80% in verification and reporting times at the end of the analytical process."

Ease of use. While the back-end of CDS software may be complex, "you don't want a CDS to be excessively complicated from the end-user's standpoint. You don't want to be jumping around delving deep into the CDS to try and find a particular function that you need. You want things to be easily accessible," Neaves feels.

For instance, having a single user interface on Chromeleon CDS has simplified the pro-

cess of setting up analyses. "Being able to set systems up with sequences of samples for analysis quickly, efficiently, accurately, reproducibly...has been critical and we've seen a great improvement," says Neaves.

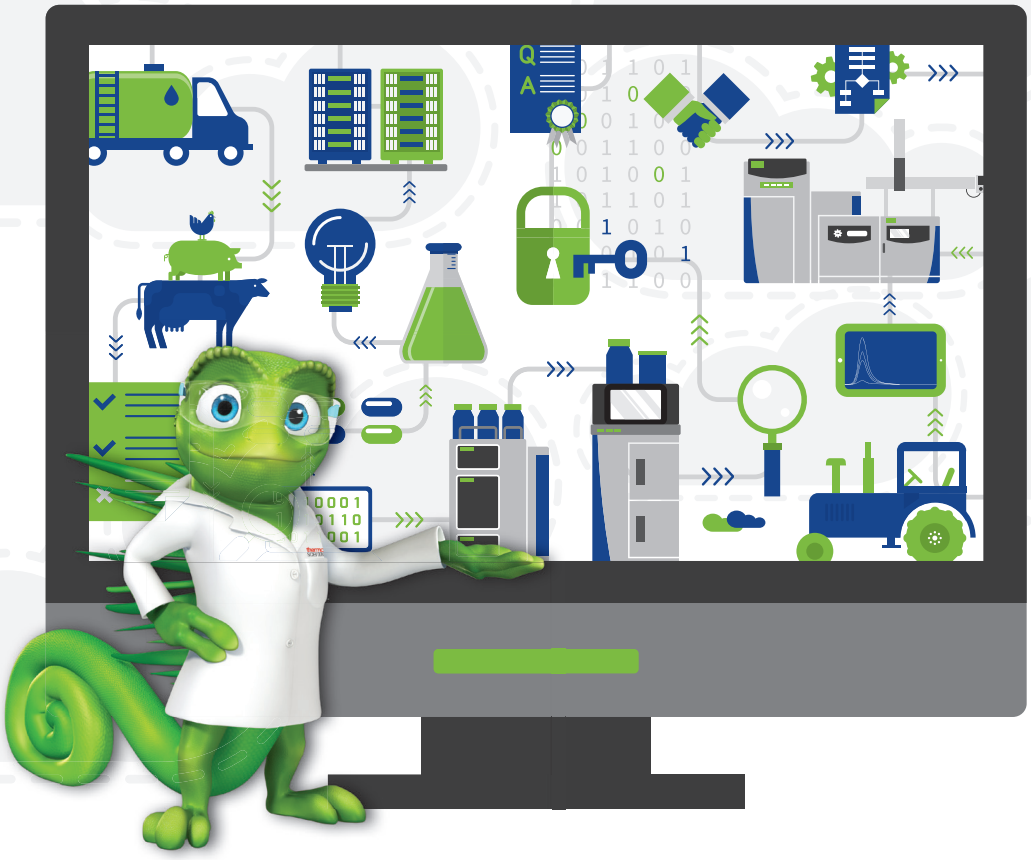
Templates are created in Chromeleon eWorkflows™ procedures, which enable operators of all skill levels to easily set up a run, including sequence, methods and reports. This is particularly important when samples have multiple components being measured simultaneously. Broughton Laboratories pharmaceutical support team works with samples from solid dose, liquids, injectables and animal feeds, and it's not uncommon to detect up to 14 components in a single ENDS sample. The templates reduce the possibility of errors, ensure that only validated methods are used for the measurements, and save considerable time.

Such speed, accuracy, and consistency of analysis are essential to Broughton's clients. "With the CDS's workflows and templates, we get confidence about the integrity of the data we are collecting and reporting. The CDS helps ensure errors—from methods being used incorrectly or being altered—are minimized," says Lynch, who adds the traceability of the audit trails and the efficiencies gained through all the electronic signatures with massive amounts data has been invaluable. "With the amount of samples that we're putting through our group, having the modern Chromeleon software has been essential to helping us maintain speed and accuracy," states Lynch.

Broughton Laboratories uses Chromeleon CDS on a network-based system, which enables centralized data backup and avoids having different databases stored on individual computers. Lab-to-lab data comparisons and reporting across the company are much more efficient.

Summary

With improvements in data collection, processing, reporting, and storage, Broughton Laboratories has eased the growing pains of its organization through Chromeleon CDS. Being able to implement mass spectrometers into the CDS has been a huge benefit. Templates help their operators set up runs easier, faster, and with less error. Manual steps related to sample testing, results capture and analysis have been eliminated, which means increased productivity and less training. With one CDS system and one place for data storage, samples move through the streamlined workflow efficiently. And regulatory guidelines are addressed with controls for data integrity and effective system management. All in all, Broughton Laboratories has certainly discovered how to put the advantages of ThermoFisher's Chromeleon CDS to good use.



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Ensuring Data Integrity and Compliance with a Modern Chromatography Data System

Interview with Shaun Quinn

Regulators worldwide are placing an increased emphasis on data integrity shortfalls. While nearly all pharmaceutical laboratories are aware that data integrity must be maintained throughout the lifetime of a drug product, some critical practices that ensure compliance are falling through the cracks. Here, Shaun Quinn, Marketing Manager of Compliance, Chromatography Software, focusing on eRecord regulations and compliance at Thermo Fisher Scientific, talks with *LCGC* about challenges that laboratories face in terms of maintaining data integrity and, importantly, how they can improve efficiency and maintain compliance with a modern chromatography data system (CDS).

LCGC: What sorts of data integrity challenges does a typical GMP lab face today?

Quinn: Overall, the renewed focus on data integrity from regulators has forced laboratories to review their processes, controls, and systems to reassess the reliability of the data they generate. Laboratories must evaluate, for instance, whether sufficient checks are in place to ensure data is collected, recorded, and evaluated properly. This includes determining whether or not the so-called "Four-Eyes Principle" is being applied appropriately, particularly where there are instances of self-recorded data.

The emphasis on data integrity has also forced laboratories to scrutinize orphan data, which are data where results are acquired, but not reported or reviewed. For instance, test injections may be performed by a chromatographer prepping the instruments. But often, the results of the test runs are never included—intentionally or unintentionally—in any reports or investigations of atypical results. To ensure data integrity, laboratories must ensure that all of these data are included in their reports.

Another challenge with electronic systems is regarding data management and oversight. Laboratories must ensure that changes to records and settings are

only made by authorized personnel and that all those changes are also recorded. Laboratory managers are responsible to the business owners, ensuring that all operations comply with the policies and procedures required by regulators. Thus, personnel training, particularly around the electronic systems, is a critical area, in addition to ensuring the staff has the education and experience to perform their required duties. Separation or segregation of duties is an important concept to demonstrate control; for instance, the rights and responsibility to delete data should fall on somebody who has no involvement with the data that has been acquired. The recommendation is that laboratories assign those kinds of privileges to IT personnel only.

A last major challenge to laboratories that data integrity has brought forward—and one that labs had not committed much resources to in the past—is regarding audit trail review and ensuring that it is done along with the data review. Many regulated companies are looking for technology solutions and strategies for audit trail reviews.

LCGC: Regarding your last point about audit trail reviews, what should they be looking for and how frequently should they do reviews?

Quinn: Regulated companies have to break down the audit trails and understand the context and relationship with the business processes. There will be those that record actions around the data that are acquired on a daily basis. Then, you have the more administrative audit trail review requirement, which involves the management of the system, the users, actions, possible attempts at falsification, and other similar factors. The risk associated with the various audit trails determines the frequency of the review. Quite often, at batch release, you will do a routine review of the audit trails and check, for instance, all of the metadata, especially manual changes made by an analyst; dilution factors, weight changes, and manual integration. Other data, like checking privilege changes against training records, can be checked bi-annually. Again, the frequency of checking is associated with risk.

LCGC: Regarding data integrity, what exactly are regulators most concerned about?

Quinn: Based upon what our customers are saying and the review of official observations, regulatory authorities are concerned with a lack of basic access control and security measures around electronic systems.

Now, 20 years after 21 *CFR* Part 11, many software vendors have the necessary controls in their systems. Sometimes, the problem comes down to users not implementing them correctly, however.

I've seen cases of shared user logins, where several people are logging into the system with one generic account. Shared logins are not permitted in the

regulations; everything must be attributable to individuals.

Moreover, some people are not enabling the audit trails or are disabling this function. This arises from individuals not implementing the privileges necessary to prevent people from disabling audit trails, but it's a requirement that everybody must control appropriately.

Regulators are also finding problems with contemporaneous activities. Analytical data must be recorded at the time the analysis is performed. Analysts or operators only recording activities after they've done five or six steps in a process is wholly unacceptable when they should be recording their actions and the results or output at each step in that process. Some regulated companies are also not investigating atypical or out-of-specification data through their quality management systems.

Testing into compliance is another problem, where people may run a prep sample when equilibrating the chromatographic system. They then use the run to make small modifications to the system to improve the output: the chromatogram.

Regulators fully expect that analysts need to equilibrate the systems. But when they do, either a reference standard or something that relates to the reference standard should be used—not a product sample. And, they must report that information and never hide it. Other examples of testing in to compliance relate to some firms using integration wrongly without specification to manipulate the final result.

One last problem is the deletion of original data. Deleting any data and any falsification of the data should not be done.

LCGC: How might modern CDS software help address some of these challenges?

Quinn: Wherever human intervention exists in any process within the laboratory, there always seems to be a higher risk that procedures are not strictly followed. Sometimes, controls are in place, but they simply are not strict enough to enforce data integrity practices.

Modern CDS software in laboratories provide the required technical controls that either prevent many of these human error issues or at least provide controls that can detect problems through audit trails and other such measures.

For instance, through automated electronic systems, you can restrict access or force every user to have his or her own login. You can ensure that any entries, changes to critical data, and modifications are attributable to a specific person. A modern CDS can also highlight situations where those critical data have been manually entered and changed. It provides much more operational control around the processes that involve the analyst.

LCGC: Could you talk about some features of the Chromeleon CDS software that may help laboratories with compliance or productivity?

Quinn: Many issues come from a lack of understanding, knowledge, or experience

with the system. So, one major benefit of Chromeleon CDS is its ease of use, which was one of the design principles. Chromeleon software is easy to understand and the user interface is relatable to common software that analysts use on a daily basis.

With Chromeleon CDS, problems are easier to detect and the system minimizes human errors. When analysts have a clear understanding of the interface, they can be up and running very quickly and you can minimize many problems (especially those relating to data integrity). The Chromeleon software's architecture facilitates many of those benefits. An example is when you're reviewing data and metadata, including the audit trails. Chromeleon software simplifies the chromatographic process via sequences. A sequence contains the injection list that maintains the order in which injections are analyzed. It includes the injection results (chromatographic raw data and the acquisition metadata) and also all of the associated methods involved such as the instrument method, processing method, report templates and any spectral libraries.

It incorporates metadata (e.g., sample weights and dilution factors), including all versions of all objects, with complete auditing (Data and Injection Audit Trails) to describe the full history of the Sequence. It provides an easy means to look at your final result and understand who, when, what, why changes were made during the actual analysis of a chromatographic run.

Chromeleon software has dedicated user management that is designed for the chromatographic workflow. We wanted to minimize human intervention wherever we could. The system not only has built-in automated qualification for the software, but also for the instrument. When we automate much more of the process, there are less errors and less paperwork.

Another key advantage of Chromeleon CDS in this data integrity environment is that audit trails are segregated according to their relevance, which gives them clear context. So, that it's easier for users to review, interpret, and understand rather than just have a big, long list to work through.

LCGC: What have been the latest developments made to Chromeleon CDS?

Quinn: We are constantly improving the Chromeleon CDS system. We listen to all of our customers' requests and use them to provide the best tools for increasing efficiency in the lab and maintaining compliance standards—all while keeping

up with the latest regulatory thinking. For example, FDA recently expanded its definition of what the audit trail should encompass. In addition to data changes, modifications, deletions, they want to look at any system events (possible changes that can happen externally to the software that can impact data). So, in Chromeleon CDS, we introduced an additional level of security on the actual chromatographic raw data. We basically applied a cryptographic hashing around the file. The file is in a secure location out-of-the-box, but if somebody did ever manage to get to that location and wanted to try and copy, move, or change that chromatographic raw data, Chromeleon CDS can detect changes and verify the integrity of the raw files. The system also records these events inside the audit trail and notifies the users that there's a problem with the integrity of the data file.

LCGC: What features should labs look for when they're evaluating CDS systems?

Quinn: In addition to the software, laboratories have to look at suppliers and the latest regulations in a much more detailed manner. Look for suppliers with a clear understanding of regulated companies' needs and who are open to on-site supplier audits.

Customers also must invest in validation. For many, it's just a documentation exercise. But with the focus on data integrity, the validation will not just help you document and have evidence that a system is fit for purpose, but it will also help you understand and improve the processes and controls around the CDS.

Now, when you evaluate the CDS, make sure it has the required fundamentals and controls to comply with the mandatory regulations such as 21 CFR Part 11. Again, data integrity puts a strong focus on audit trails. So, you need to evaluate the audit trail controls that the CDS provides and ensure that you can establish a documented process for the review of the audit trails.

Also, consider the degree of effort the CDS needs to configure, access, and interpret the electronic audit trails. It can vary greatly by system and vendor. Look at the electronic audit trails solutions, how they differ, and the functionality they provide. For each function, you should be able to search, sort, filter, and report the information out of the audit trails.

Having a CDS with all these audit trail functionalities will help increase a laboratory's efficiency and help ensure it maintains regulatory compliance.

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