LC GC

UBM

Data Integrity in the GxP Chromatography Laboratory, Part 2

OCTOBER 2018

Calculation of the Reportable Results
Mark E. Newton and R.D. McDowall

Second-Person Review
Mark E. Newton and R.D. McDowall

Open Culture, Training, and Monitoring Metrics
Mark E. Newton and R.D. McDowall

Sponsored by

Agilent Technologies

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

485F US Highway One South, Suite 210,
Iselin, NJ 08830
(732) 596-0276

LCGC North America (ISSN 1527-5949 print) (ISSN 1939-1889 digital) is published monthly by UBM Life Sciences, 131 West First Street, Duluth, MN 55802-2065. *LCGC Europe* (ISSN 1471-6577) and *LCGC Asia Pacific* (ISSN 1754-2715) are published monthly by UBM EMEA, Hinderton Point, Lloyd Drive, Cheshire Oaks, Cheshire CH65 9HQ, UK. Issues are distributed free of charge to users and specifiers of chromatographic equipment.

To subscribe, call toll-free 888-527-7008. Outside the U.S. call 218-740-6477.

Agilent OpenLab

Increase Productivity While Meeting Data Integrity Requirements

Upgrade to Agilent OpenLab CDS

Choosing the right data system can make all the difference. OpenLab CDS is a single, secure chromatography data system for chromatography and single-quadrupole MS workflows that enables you to streamline laboratory operations and efficiently generate quality results.

OpenLab CDS ensures data integrity and facilitates rigorous regulatory compliance with your choice of technical controls—such as audit trail review, access control, records protection, and e-signatures.

Learn more about Agilent OpenLab CDS.

www.agilent.com/chem/openlabcds-streamline

Agilent

INTRODUCTION

Analytical laboratories have a lot to consider in terms of designing best practices for ensuring data integrity. To help, *LCGC* has published a six-part series authored by Mark E. Newton, the principal at Heartland QA, and R.D. McDowall, the director of RD McDowall Limited, who offer rules and best practices for ensuring data integrity.

Reprinted in this ebook on *Data Integrity in the GxP Chromatography Laboratory, Part Two* are the last three articles in the *LCGC* series by the same name. The set presented here, authored by Newton and McDowall, are intended to help laboratories ensure quality work with practical guidelines about several areas of data integrity.

First, Newton and McDowall cover considerations for the calculation of reportable results with chromatographic data. Next, the pair discusses the second-person review process for regulated records and the risks to be addressed. The ebook rounds out with a discussion about three practices laboratories can adopt to maintain data integrity: having an open culture, conducting data integrity training, and producing quality and data integrity metrics.

Readers interested in reviewing the first three articles in the series can access the companion ebook, *Data Integrity in the GxP Chromatography Laboratory, Part One.* Topics covered include sample preparation, collection, transport, and receipt for chromatographic analysis, avoiding manual processes, and how to correctly set up an instrument, run system suitability test samples, and acquire data.

Calculation of the Reportable Results

Mark E. Newton and R.D. McDowall

Calculation of reportable results from chromatographic analysis is an important area where data integrity may be deliberately or unknowingly compromised.

This is the fourth of six articles on data integrity in a regulated chromatography laboratory. The first article discussed sampling and sample preparation (1), the second focused on preparing the instrument for analysis and acquiring data (2) and the third discussed integration of acquired chromatograms (3). In this article, we reach the end of the analytical process and focus on the calculation of the reportable results.

Scope of Chromatographic Calculations

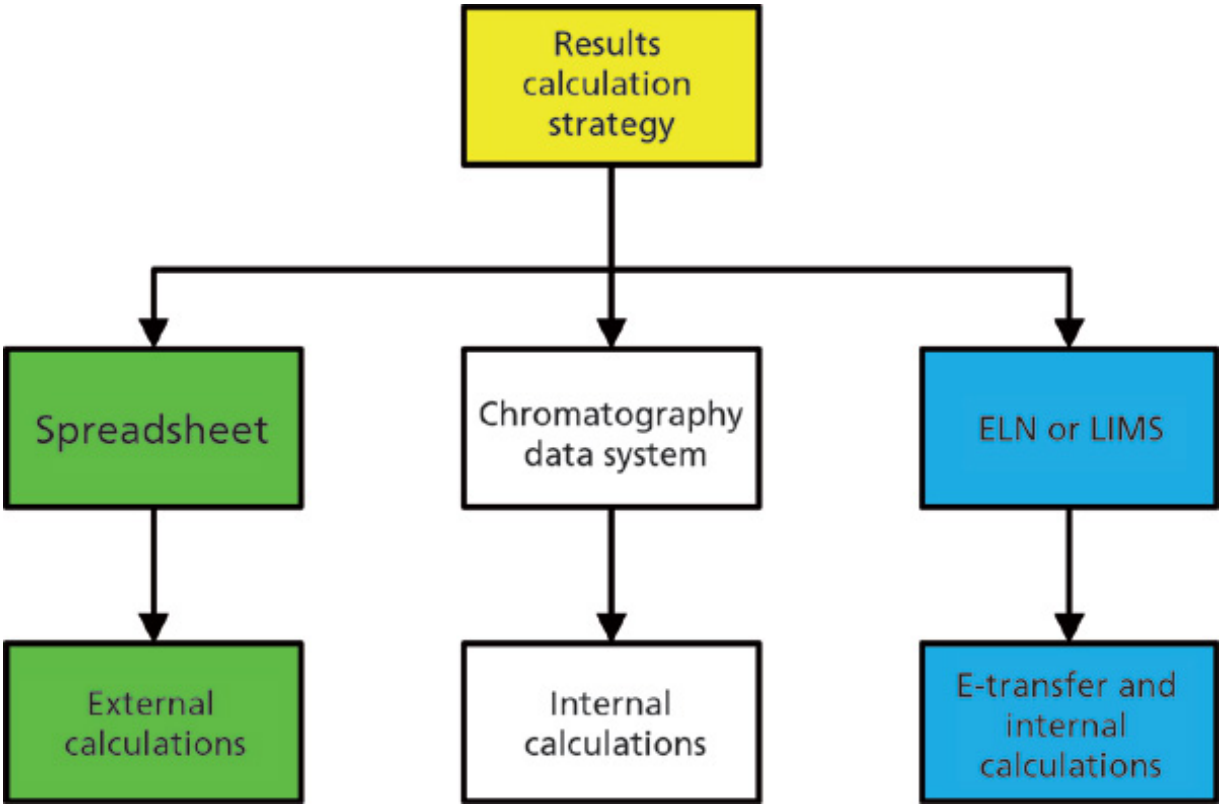
What does calculation of the reportable results involve with chromatographic data?

- calculation of system suitability test (SST) parameters and comparison with the acceptance criteria
- calibration model and calculation of initial results from each sample injection including factors such as weight, dilution, and purity
- calculation of the reportable results from the run.

Where do these calculations take place? There are three main options to consider:

- Within the chromatography data system (CDS) application, suppliers have developed the models and tools to incorporate most calculations required by laboratories.
- Peak areas can be transferred electronically to a laboratory information management system (LIMS) or electronic laboratory notebook (ELN) to perform the calculations.
- Print the peak areas and manually enter them into a (validated?) spreadsheet or external application, such as a statistical application.

Figure 1: Options for calculation of reportable results.



These options are shown in **Figure 1.** Note that we have omitted the use of a manual calculator, because this option is just too error prone for serious consideration in today's regulatory environment.

General Considerations for Calculations

It is worthwhile to start our discussion by defining the characteristics of calculations performed in a robust, compliant manner:

1. Calculations must accurately reflect the true state of the material under test.
2. The calculations and any changes, either before or during result calculations, must be documented and available for review.
3. Calculated values should not be seen by the analyst until the value has been recorded in permanent medium. This step includes an audit trail of the event.
4. After initial calculation, changes made to factors, dilutions, and weights used in calculation must be preserved in an audit trail.
5. All factors and values used in the calculation must be traceable from the original observations or other source data to the reportable result.

No matter where calculations happen, it must be possible to see the original data, the original calculation procedure (method), and the outcome. In addition, there must be sufficient transparency so that any changes to factors, values, or the calculation procedure are captured for review. A bonus would be an application that flags changes made to any of the above after initial use of the calculation procedure—this flag tells the reviewer that audit trails should be checked to assess the scientific merit of the change or changes.

Making a Rod for Your Own Back

Of the three options shown in Figure 1, many laboratories choose the spreadsheet. Despite the efforts of CDS application suppliers to provide a seamless way to automate calculations, many laboratories will select the least efficient and the least compliant option. Why is this? Comfort, as most people know how to generate a spreadsheet. Why bother to read the CDS, LIMS, or ELN manual and implement the option that often is the quickest, easiest, and best from a data integrity perspective? Instead, the laboratory is committed to supporting the paper industry through printing all data, entering the values manually, and employing second person reviewers to check for transcription errors.

Better Data Integrity Alternatives 1: Calculations in a CDS

The chromatography data system itself is often the best location for calculations. It usually provides access control to prevent unauthorized changes, versioning of calculations, and audit trail reviews for changes in calculated values and to the calculations themselves. In addition, the calculations are in the same system that holds the original (raw) data so that review is usually within one system. There are some data integrity risks, however:

> **"The chromatography data system itself is often the best location for calculations."**

- Some chromatography data systems will allow analysts to see calculated values (for example, plates or tailing) before they are committed to the database, permitting an analyst to process (or reprocess) data without leaving audit trail records of the activity.
- Factors, weights, and water weights (for anhydrous results) must either be entered manually or through an interface—more on this later.
- On the negative side, there are calculations that are difficult to perform directly in the chromatography system, such as statistics across multiple injections within a test run or across multiple runs. In these situations, often a spreadsheet is used to perform these calculations

Better Data Integrity Alternatives 2: Calculations in LIMS or ELN

LIMS and ELN applications, if configured correctly, generally have audit trail capabilities for most analyst actions and have the capability to perform calculations that are problematic for chromatography applications—such as the cross-run calculations mentioned above. Calculations like these are where a LIMS will shine. Access controls to prevent unauthorized actions and versioning of calculations are also available in a solid LIMS or ELN application.

On the dark side, the ability to interface is a process strength and data integrity weakness. Data sent into LIMS or ELN can be manipulated externally, then sent to the LIMS or ELN for calculation. The other weak point for a LIMS or ELN is also a weak point for chromatography calculations: manually entered factors or weights. Any time a human manages a numeric value, there is a risk that digits in that number will be transposed in about 3% of transactions (4). Another point to consider: a LIMS or ELN can perform calculations such as best-fit linear regression for standard curves, but more work is required to set up the calculations in a LIMS or ELN versus the chromatography system. In this case, the LIMS or ELN is more flexible, but the chromatography system is better adapted to a process it performs routinely.

Calculations Using External Applications

Last (and certainly least) is the humble spreadsheet. Before performing any chromatography calculations with a spreadsheet, read the "General Considerations for Calculations" section above. After reading, answer this question: Which of the general considerations is met with a spreadsheet? None, you say? You are correct. A case could be made for using a validated spreadsheet. That might be true, assuming someone doesn't unlock the sheet and manipulate the calculations (you did lock the cells and store the sheet in an access-controlled folder, correct?). Although it might be more "comfortable" to calculate results from a spreadsheet, it is worth the effort to put those calculations in the chromatography system. In addition to providing no access control or audit trail, a spreadsheet typically has manual data entry and permits an analyst to recalculate results before printing and saving the desired result values for the permanent batch record.

Some LIMS and ELN systems permit analysts to embed spreadsheets within the system, to overcome the security limitations and missing audit trail capabilities of desktop spreadsheets. If spreadsheets are to be used at all, this approach would be the preferable manner to deploy them.

A Calculation Strategy

It is advisable to create a general strategy for handling calculations. The strategy should specify the types of data and where calculations are best performed. Such a strategy permits personnel at different sites to create relatively consistent electronic methods. The strategy need not be complex; it could be as simple as a table or appendix in a method develop-

TABLE 1: An example calculation strategy

Data	Application Calculated and Stored	Notes
Sample dilution factors	LIMS or ELN	Manual entry in e -method and transferred to the CDS
Sample weights	LIMS or ELN	Direct interface to balance and transferred to the CDS
Conversion factors	LIMS or ELN	Manual entry in e -method and transferred to the CDS
System repeatability	CDS	
Standard variance	CDS	
X-intercept	CDS	
Peak area ratio	CDS	
Related substances (impurities): total amount	CDS	All areas within an injection
Related substances (impurities): largest individual	CDS	All areas within an injection
%RSD across analytical runs	LIMS or ELN	Multiple runs transferred from CDS to LIMS or ELN

ment or validation procedure as shown in **Table I.**

Key Elements for Calculations

Wherever a calculation is used, be it from a CDS, ELN, or LIMS, the mathematical formula must be specified plus any translation into a linear string used in the application as well as the data to be used in the calculation. The data used must have the format of the data plus the ranges—for example, for pH values the format would be X.YY with an input range of something like 4.00–8.00. It is important to ensure that not just values within specification are considered but also data outside of it. The calculation needs to be tested with datasets within as well as at and outside any limits before being released for use.

Knowing how data are truncated and rounded is essential, especially when the result is used to make important decisions. The standard practice should be, "Do no truncating or rounding until the last step (which usually is the individual aliquot result or ideally the reportable result)." Before rounding, preserve all digits.

There may be scenarios where rounding or truncating of digits will happen because of technical issues, such as data reprocessing on different platforms, processors, or applications. When this adjustment happens, it is imperative that the amount of bias be understood, and its

potential impact on business decisions be estimated.

Rounding and Precision of Replicates and Final Result

Reportable replicates or final results should be rounded to the same number of decimals as the specification to which they are compared. When there are multiple specifications, such as a regulatory and a release specification, then choose the specification with the largest number of decimal places for the rounding decision. In the absence of a specification, an accepted practice is to round to three significant figures.

Manipulation of Calculations

In well-controlled chromatography applications with audit trails enabled, the primary place for data manipulation is interfaces, both human and machine. Values can be manipulated outside the system, then keyed in as the correct value and used to bias reportable result values. For example, USV Ltd received a warning letter in 2014 for entering back-dated sample weights into calculations (5). Values can be manipulated outside another system—or even within that system—and then sent to chromatography using validated interfaces and accepted for processing as genuine values. In some respects, the latter situation is worse, because the manipulation is two or more steps removed from chromatography, and therefore more difficult to detect. Only by reviewing data back to the point of creation (raw data), can potential issues be detected and prevented within the analytical process.

Reporting Results

The reportable result, defined by the FDA as one full execution of an analytical procedure (6), is specified by either the applicable method or specification. Difficult questions arise when the final result meets specification but one of the replicates used to determine the reportable result is out-of-specification (OOS) or out-of-trend (OOT). These individual results are also classified as OOS and must also be investigated (6). Interestingly, most laboratories testing into compliance or falsifying results do not have any OOS results: One company had zero OOS results over a 12-year period (7). Most laboratories do not falsify results to make them OOS, unless they are very stupid.

Although OOS, OOT, and out-of-expectation (OOE) results receive attention from analysts and inspectors, it is important to recognize that falsification activities are directed at the opposite: making test results that would fail the specification into passing results through various forms of data manipulation. This probability of extra scrutiny makes it prudent to give careful review to results that are near specification limits (say, within 5%), to verify that all changes and calculations are scientifically justified.

With a hybrid CDS, most laboratories print all data rather than simply a summary, which makes it harder for the second person to review. Instead, just print a summary and leave the majority of data as electronic, thus facilitating a quicker review process (8).

Monitoring Metrics

Metrics generated automatically by a CDS application can be generated during the analytical phase of the work. The topic will be discussed in part VI of this series on culture, training, and metrics. In addition, we have written a paper that was published in 2017 in *LCGC Europe* on this subject of quality metrics as background reading on the subject (9).

How Can We Improve?

Direct interfaces between analytical systems can help reduce the potential for human manipulation of calculation factors. It is imperative to recognize the fundamental truth that every interface is a potential data integrity issue, and take appropriate steps to secure interfaces and the data they are transferring. One special area of concern is the system collecting the original data values: Does it permit users to create data values over and over, then select the value to be stored? Unfortunately, this is the situation for many benchtop analytical instruments and it supports the noncompliant behavior of testing into compliance. Until analytical instruments evolve in their technical design, we must rely on training, laboratory culture, and second-person observation (witness) of critical data collection to minimize the potential for this behavior (10–13).

As mentioned in the first article in this series, the preparation and recording of dilution factors is an area for improvement in integrity. Many laboratory practices still rely on analysts to manually record the dilutions that were prepared before testing. Moving these manual dilutions into procedures with gravimetric confirmation can increase confidence that dilutions were correctly prepared. It also provides a trail of objective information for investigating if result values must be investigated for failure to meet acceptance criteria or product specifications.

Is Management the Problem?

Management can create a climate where personnel are encouraged to manipulate test results. Such an environment is not created directly, but indirectly through operational metrics. Mandates like "zero deviations," "no product failures," and "meeting production targets" are each sufficient to encourage data manipulation; throw in the possibility of a demotion or dismissal for failing to meet any of these mandates and the environment is ripe for data manipulation to ensure that mandates are met—regardless of the true condition. The irony of this environment is that two losers are created: the patient who receives sub-standard product, and the company that no longer knows its true capability or process trend. This phenomenon is recognized by the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) data integrity guidance, warning that management should not institute metrics that cause changes in behavior to the detriment of data integrity (14).

Summary

Calculations and reporting are the place where raw data, factors, and dilutions all come together to create reportable

values. It is critical that calculations be preserved from the first attempt to the final reported value, because of the potential for improper manipulations. This policy is essential when a second person comes to review all work carried out, as we shall discuss in the next part of this series.

References

(1) M.E. Newton and R.D. McDowall, *LCGC North Am.* **36**(1), 46–51 (2018).

(2) M.E. Newton and R.D. McDowall, *LCGC North Am.* **36**(4), 270–274 (2018).

(3) M.E. Newton and R.D. McDowall, *LCGC North Am.* **36**(5), 330–335 (2018).

(4) R.D. McDowall, *LCGC Europe* **25**(4), 194–200 (2012).

(5) US Food and Drug Administration, "Warning Letter, USV Limited" (WL: 320-14-03) (FDA, Silver Spring, Maryland, 2014).

(6) US Food and Drug Administration, *Guidance for Industry Out of Specification Results* (FDA, Rockville, Maryland, 2006).

(7) US Food and Drug Administration, *483 Observations, Sri Krishna Pharmaceuticals* (FDA, Silver Spring, Maryland, 2014).

(8) World Health Organization (WHO), *Technical Report Series No.996 Annex 5 Guidance on Good Data and Records Management Practices* (WHO, Geneva, Switzerland, 2016).

(9) M.E. Newton and R.D. McDowall, *LCGC Europe* **30**(12), 679–685 (2017).

(10) R.D. McDowall and C. Burgess, *LCGC North Am.* **33**(8), 554–557 (2015).

(11) R.D. McDowall and C. Burgess, *LCGC North Am.* **33**(10), 782–785 2015).

(12) R.D. McDowall and C. Burgess, *LCGC North Am.* **33**(12), 914–917 (2015).

(13) R.D. McDowall and C. Burgess, *LCGC North Am.* **34**(2), 144–149 (2016).

(14) PIC/S PI-041 Draft Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments (PIC/S: Geneva, Switzerland, 2016).

Mark E. Newton is the principal at Heartland QA in Lebanon, Indiana. Direct correspondence to: mark@heartlandQA.com.

R.D. McDowall is the Director of RD McDowall Limited in the UK. Direct correspondence to: rdmcdowall@btconnect.com

This article first appeared in LCGC North Am. ***36*** *(7), 458–462 (2018).*

Address the Paradigm Shift in Regulatory Inspections

ON-DEMAND WEBCAST Aired June 28, 2018

View this free webcast at www.chromatographyonline.com/lcgc_p/inspections

EVENT OVERVIEW:

The term "FDA audit" can trigger many responses, including dread and panic. It also raises many questions. What triggers a regulatory audit? How has the FDA changed its auditing strategy and what are they focused on? What systems are likely to get inspected? In addition to answering these questions, this webcast will focus on ensuring data integrity in an analytical laboratory. Join us to learn from Humera Khaja, Agilent's software compliance expert with nearly a decade of regulated software experience.

Webcast participants will learn about:

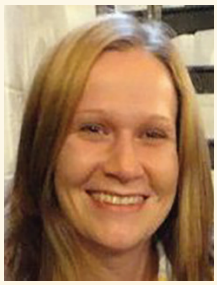
- How FDA inspections have changed
- FDA's goals during an inspection
- The potential systems that may be subject to inspection
- Suggested mechanisms to ensure data integrity in analytical labs
- What type of documented evidence is required to prove that software application systems are validated

Who Should Attend

- Lab managers
- Chemists
- Scientists
- Technical specialists working in industries subject to FDA audits

Presenters

Humera Khaja
Software Compliance Program Manager
Informatics Division,
Agilent Technologies



Moderator

Kate Mosford
Managing Editor
LCGC

Sponsored by

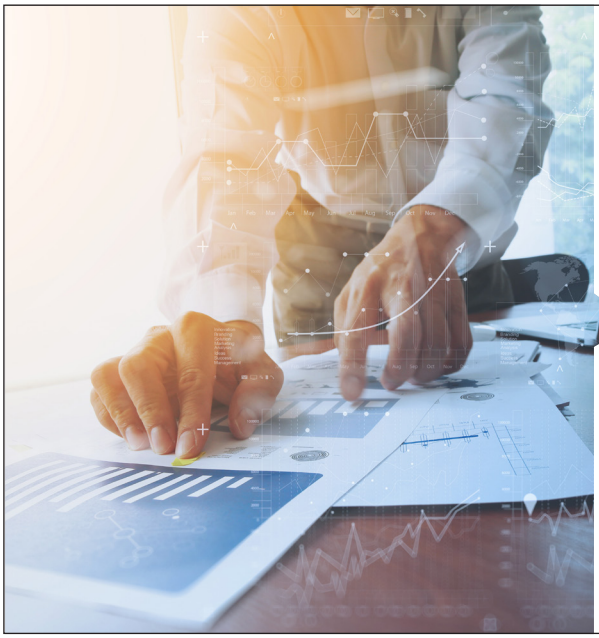
Agilent

Presented by

LCGC

BACK BY POPULAR DEMAND

For questions contact Kristen Moore at kristen.moore@ubm.com



Second-Person Review

Mark E. Newton and R.D. McDowall

The fifth article in this series discusses the second-person review process for regulated records and the risks to be addressed, such as reviewing all data in the run, including aborted or rejected data. The added review costs (and time) of hybrid records and paper logbooks is illustrated. Common failure modes for review are identified. Finally, some management behaviors that compound an already complex step are described along with their consequences.

This article is the fifth of six on data integrity in a regulated chromatography laboratory. The first article discussed sampling and sample preparation (1), and the second focused on preparing the instrument for analysis and acquiring data (2). These articles were followed by the third part, which examined the integration of acquired chromatograms (3), and the fourth installment, where we discussed the calculation of the reportable results (4). In this article, we consider the second-person review of all the data, and records generated in the process.

Regulatory Requirements for a Second-Person Review

One of the keys to data integrity in a regulated laboratory is an effective second-person review, and its importance is reinforced by the Food and Drug Administration (FDA) and European Union Good Manufacturing Practice (EU GMP) regulations:

> 21 *CFR* 211.194(a) Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards,including examinations

and assays, as follows:
(8) The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards (5).

6.17. The tests performed should be recorded and the records should include at least the following data:
vii. Initials of the persons who verified the testing and the calculations, where appropriate (6).

In addition to its being a regulatory requirement, the second-person review is the first-line defense of data integrity because it is the initial opportunity to discover errors and omissions in documentation and execution. In addition, it is important to note that a review is conducted by the most qualified person to assess the scientific merit of all activities taken in the preparation of the reportable result. Who is more qualified to review the dataset than an experienced scientist who knows the technical details of executing the analytical procedure?

Scope of Second-Person Review

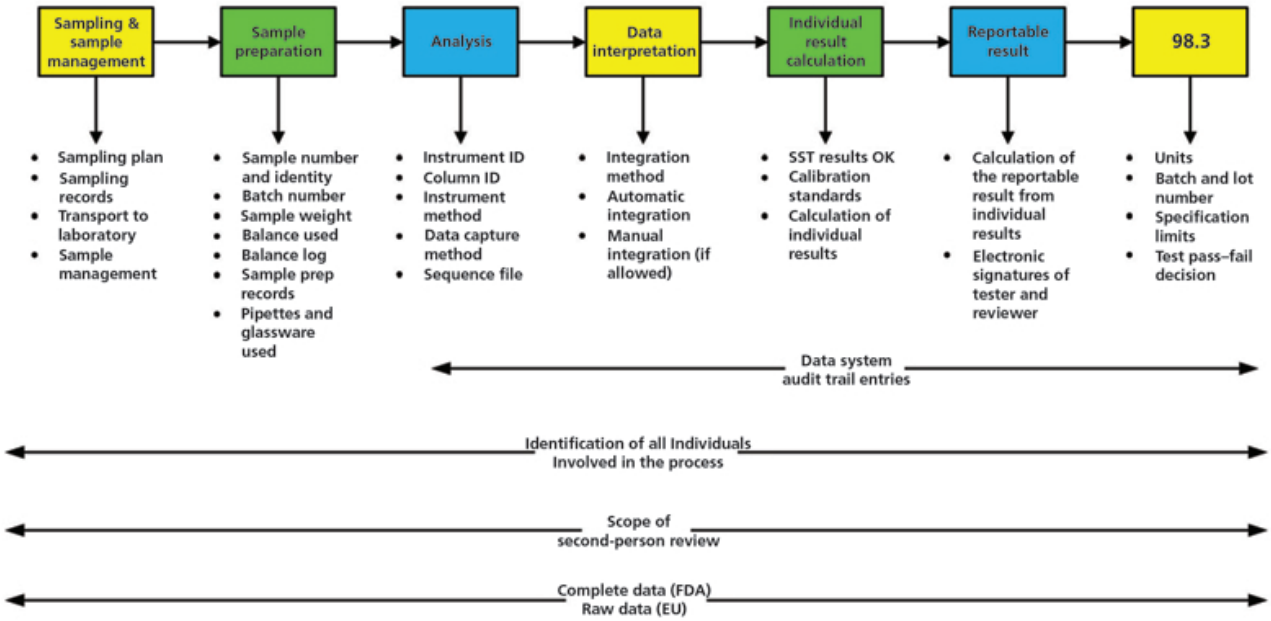
Because a second-person review is a regulated activity, it is necessary for the activity to conform to the regulations involved. One of the most important regulatory requirements is that the complete set of data must be reviewed, as noted in 21 CFR 211.194(a): "A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation" (5).

How do we interpret this requirement for a chromatographic analysis? The scope of this requirement is shown in Figure 1, and it encompasses all records from taking the sample to generating the reportable result. It consists of all records generated in sampling, preparation, instrumental analysis, data evaluation, and calculation of the reportable result, as we have presented in Parts I–IV of this article series (1–4). Also, in **Figure 1** you can see the scope of complete data (5) or raw data (6), and the scope of the audit trail review.

However, some laboratories have struggled with the term "complete," defining it as only the data directly used to calculate the reportable result. This is wrong, as it excludes data that might have been generated, but excluded from the reportable result for various reasons. It is imperative that the reason for data exclusion is scientifically justified and documented, and the reviewer should be given this data to assess the scientific merit for excluding the data from the reportable result. See questions 2, 12, and 14 in the FDA's data integrity guidance (8) for more detail on this subject. In a recent warning letter, excluded data were not given to the reviewer, resulting in a regulatory citation (9). Transparency of data is a key part of ensuring integrity in regulated laboratory operations.

Some examples of this excluded data that must be presented for second person review include:

Figure 1: The scope of a second-person review of a chromatographic analysis (7).



- Aborted runs or aborted tests
- Rejected runs that failed to meet suitability or acceptance criteria
- Runs that are out of specification (OOS) or out of trend (OOT)
- Runs that are voided for any reason (dropped injections, power failure) along with supporting evidence
- Prior calculations of result values, if performed on external applications (for example, statistical programs or spreadsheets)
- Original records containing errors that have been corrected and for which both the original and corrected printouts are being resubmitted for review.

Compiling the complete record of actions can be quite challenging, especially when multiple systems and hybrid records are involved. World Health Organization (WHO) guidance in clause 11.14 advises

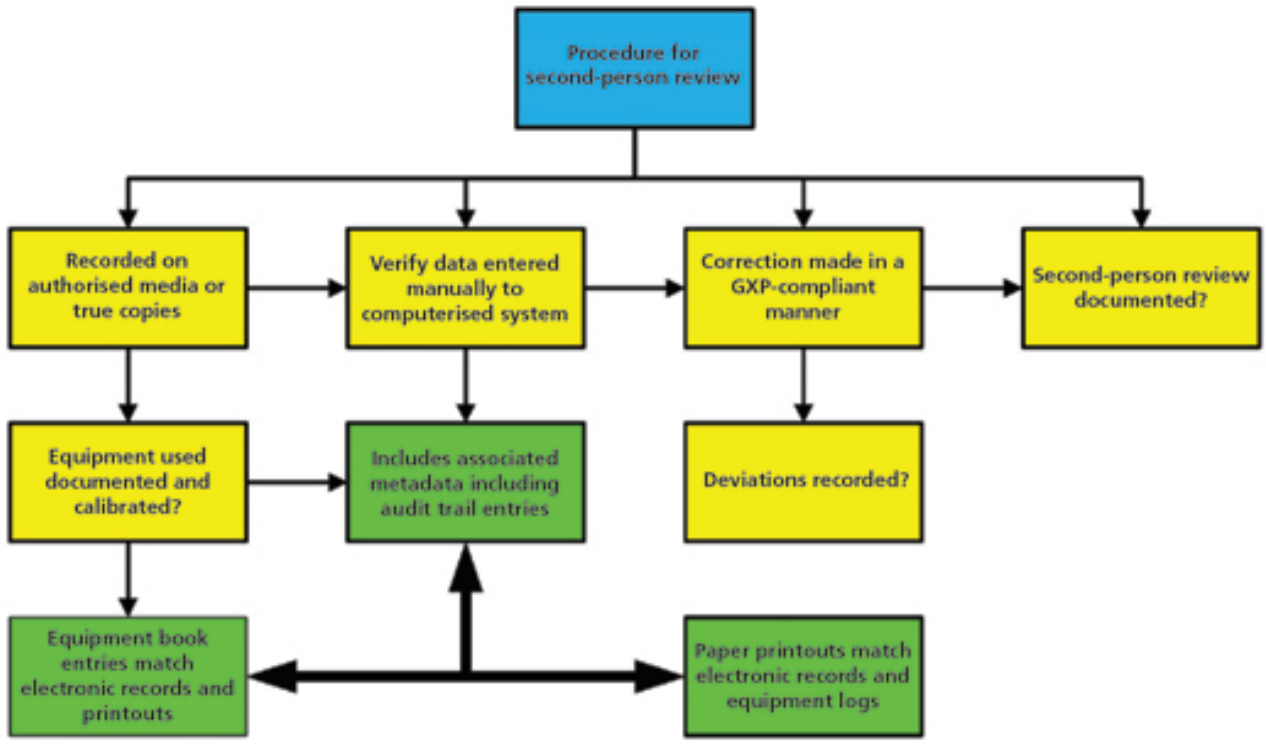
"To ensure that the entire set of data is considered in the reported data, the review of original electronic data should include checks of all locations where data may have been stored . . ." (10).

This step requires a procedure for the review.

Procedure for a Second-Person Review

A standard operating procedure (SOP), coupled with effective training, is also required for a second-person review. An outline for such a procedure is shown

Figure 2: An outline for a second-person review SOP (7).



in **Figure 2,** and includes the review of printouts from a hybrid system or even a summary from a chromatography data system (CDS) used with electronic signatures. Associated with this SOP, it is recommended that each analytical procedure have a checklist to assist reviewers in identifying the complete record of testing, because the records will vary from method to method within a laboratory. Each checklist will need to be controlled and uniquely numbered (11). Each checklist will need to be controlled and uniquely numbered (11). It may also be necessary to provide instructions on how to retrieve aborted or rejected runs from the CDS, and include them in the second-person review.

Who Should Be a Reviewer?

Selecting a reviewer is the single most critical part of the review process. Even with a robust checklist, the final quality of the review is wholly dependent on the person performing it, their knowledge and experience of the CDS functions, and the support they receive from management. The experience and demeanor of the reviewer must be up to the task. As a result, reviewers

should understand the theory and have performed the method for an extended period. They are aware of the challenging steps, and the places where errors can happen. They can look at the time taken for analysis, and tell when someone is rushing or struggling. This background and experience requirement means that reviewers will often be more senior people within the organization. In addition to the technical background, a reviewer must be detail-oriented. Reviewing requires a person to go to multiple sources of data (systems, notebooks, and so on)and tediously review records for accuracy. When a pipette was used to dispense a sample, the reviewer will stop, find the pipette logbook, and verify that it was in calibration on the date it was used in the assay. The reviewer will verify that dates, pipettor identification numbers, and entered values are not only recorded, but are also reasonable and consistent. Good reviewers are constantly evaluating what they see, noting anything that seems out of place or unusual. They are naturally curious. There are many people who possess the academic and experience requirements, but the ability to focus on detail and natural curiosity to evaluate and investigate data set the best reviewers apart from the rest of the analysts.

> **"Even well-qualified reviewers cannot be effective without the support of their managers."**

Is Management the Problem, Part I?

Even well-qualified reviewers cannot be effective without the support of their managers. Managers must ensure that adequate time and priority are given to perform thorough reviews, and they must support their findings when issues or changes must be made before test release. Nothing prevents adequate review like managers who complain about the time needed for a second-person review, especially when remediation of many systems just involves additional procedural controls that will slow the review rather than implement technical solutions that will speed up the review process.

Audit-Trail Review

One of the key aspects is the second-person review, as shown in Figure 1, is the review of audit-trail entries for all GMP-relevant changes and deletions (12). Because the laboratory records of an analysis must include complete data as required by 21 CFR 211.194(a)(5), and the record must be reviewed by a second person, as specified in 21 CFR 211.194(a) (8) (5), it follows that the second-person verification must be a complete review of the complete record of testing. The challenge in an electron-

ic, relational database world of a CDS: What is the complete record? In a paper world, the complete record was simpler to define, because there was much less information, and it was all in paper form. But even in the days of paper records, there had to be a list of papers that defined the complete record of testing. The move to electronic records seems more complex on the surface, but at the core it is really the same exercise. For example, an analyst could make a calculation error, discover it, and recompute the reported result. On paper, it was crossed off and changed following the documentation SOP. In a CDS, that same change is documented in an audit trail. So, the reviewer must look at the audit trail, or the review is inadequate. This same logic of matching paper to electronic records must be done for each method. After they are matched, you will discover that some audit trails do not need to be reviewed every time a test result is released from the laboratory. For example, a login–logout audit trail seldom has information that is critical (direct impact on reported result). This mapping exercise requires business and systems knowledge, and is best done by a team of people and documented for the benefit of all lab analysts executing the method. Simply allowing each reviewer to decide what to review is a sure recipe for inconsistency, errors, and omissions in released results. What makes an audit trail "critical"? The simplest criteria would be any audit trail with two characteristics:

1. It is required by a predicate rule, and
2. It has a direct impact on a reportable result.

Examples include changes to calculations, changed (overridden) original data values, calculation factors, sample identities, and reference standard potencies. However, this statement assumes that the audit trail entries of a CDS are understandable (13). If not, they fail the ALCOA+ test of legible.

Focus on the Instrument Logbook

A previous article (14) focused on the instrument logbook normally used for maintenance and use in chronological order. Although it is simple to create log-books to document required information about use and maintenance of instruments, they impose burdens on the organization. These burdens come into focus when performing a second-person review as shown in Figure 2. With interfaced electronic systems such as CDS and laboratory information management systems (LIMS), or a electronic laboratory notebook (ELN), the audit-trail review can be done electronically. Some systems give reviewers a flag when changes have been made to an original record, so no time is wasted looking for a nonexistent audit trail. Moving from LIMS or ELN back to source data is simple, sometimes with only a few keystrokes needed. Sample preparation, equipment, and solution records are linked from the test back to the detailed records of these activities. Electronic systems make access to information efficient and accurate.

TABLE I: Instrument logbooks to be reviewed during the second-person review

System or Instrument	Logbooks	Comments
LIMS/ELN	• Use logbook	Only needed if system cannot enforce individual accounts and roles
Analytical instrument (for example, HPLC, GC, or CE system)	• Use logbook • Maintenance logbook • Calibration logbook • Data transfer logbook	
Pipette	• Use logbook • Maintenance logbook • Calibration logbook	Some assays have multiple pipettes; there will be a set of logbooks for each one.
Balance	• Use logbook • Maintenance logbook • Calibration logbook	Some assays have multiple balances; there will be a set of logbooks for each one.
Sample or samples	• Lab receipt logbook • Sample storage logbook	

In contrast, hybrid systems with poor security have an abundance of logbooks that make test review both time-consuming and error-laden. Consider this scenario, where an analytical procedure uses an instrument, pipette, and an analytical balance and the test data are recorded manually in a simple LIMS or ELN system, as shown in **Table I.** Notice the number of logbooks to be reviewed? Each book requires time to verify the correct record for review, read, and assess the entry, and then return to the summary record. Errors or blank fields found during the review require the notebook to be returned to the offending person for correction and justification. Contrast this process with electronic systems where blank fields are flagged at the time of entry. Second-person review is one place where the expense of migrating to interfaced electronic systems returns a large dividend. It is worth pointing out that methods with several standalone electronic systems can have second-person review times exceeding the time to perform the method, excluding the added time to administer the logbooks (assign and manage). Unnecessary logbooks are created by electronic systems with data integrity gaps. For example, a

system that does not permit individual user accounts with passwords—a regulatory expectation— must be mitigated by creating a use logbook. The need for this logbook is completely avoided by replacing such a system with one using individual accounts and passwords.

Recording the Review

It is necessary to leave evidence of a completed review as shown in Figure 2. Sadly, many systems in use today provide no transaction to capture this evidence in an electronic format, forcing the users to document their review in hybrid form. This process is inefficient and must be a major consideration when purchasing a new system.

Hybrid or Electronic CDS?

With the use of external spreadsheets or other applications to support the business workflow, and the use of paper logbooks for equipment, organizations often find themselves with a hybrid record scenario. This represents the worst of all possible worlds for data life cycle management and second-person review. As mentioned above, the hybrid process for second-person review is cumbersome and time consuming. Consequently, more effort (and time) is required for a thorough review of the complete data. This extra effort, required for every test, becomes a temptation: It is far easier to skip a few records—for example, the pipette calibration logbook—and save some time in review. Then, add a rationalization: "After all, how often has it failed?" Hybrid records are faster to create than pure electronic records, but after their creation they carry a very heavy cost for the remaining portion of the data life cycle. If the inefficiency and increased risk of missed errors is not enough, there is the regulatory reason to avoid hybrid records. WHO TRS 996 Annex 5 on page 203 states the World Health Organization's position (10): "In the hybrid approach, which is not the preferred approach, paper printouts of original electronic records from computerized systems may be useful as summary reports if the requirements for original electronic records are also met." To rely upon these printed summaries of results for future decision-making, a second person would have to review the original electronic data and any relevant metadata such as audit trails, to verify that the printed summary is representative of all results. This verification would then be documented and the printout could be used for subsequent decision making. Given the hidden costs and preferences of regulators, it is wise to do everything possible to shift processes to electronic records, and reduce paper– electronic links to the minimum possible number.

What Can Possibly Go Wrong?

If conducted correctly, a second person review is a value added activity for any laboratory giving confidence in the analytical results and any decisions taken with them. However, review failure is possible, and it can come from four primary sources:

Failure to provide the complete record of testing for review

The responsibility for this failure belongs mostly to laboratory analysts (9). However, a portion arises from management failing to define the compete record and training people to provide it.

Failure to assess the complete record during review, including all associated audit trails, logbooks, paper and electronic records

This failure mode mostly belongs to the reviewer, but a portion is caused by the lack of a checklist that leads them to a complete review of all relevant records; the checklist is a management failure.

Failure to provide adequate time to perform a second-person review

This failure mode is mostly the responsibility of management, but a portion could be because of a lack of priority given by the reviewer (4).

Failure to assign qualified and trained people to the duty of second person review

This failure mode belongs squarely on the shoulders of management.

In total, two of the four primary failure modes belong to management, and the other two have a secondary responsibility to management. Yes, management has significant control over the quality of any second-person review, for better or worse.

Is Management the Problem, Part II?

As we can see above, management can adversely influence a second-person review. Are there other areas where management can also impact a review for the worse? Here's a nonexhaustive list:

- Inadequate recognition or reward for good reviewers—the more errors caught is a good indicator of reviewer performance rather than bad
- Inadequate time given for quality review and issue follow-up
- Complaints about time required to test, review, and release with no effort to improve the process (such as electronic systems)
- Procedural controls implemented because they are quick and cheap compounded with the failure to invest versus superior and faster technical controls

Therefore, to ensure effective second-person reviews requires management to provide the time, the training, and the tools.

Summary

A second-person review is an essential scientific and regulatory requirement for ensuring data integrity. However, this process requires the right people and the right understanding of the scope of the data and records to be reviewed for completeness, consistency, and accuracy. Reviews can be hindered by management who fail to invest in electronic systems with technical

controls to ensure speedy reviews. Without working electronically, a good review can take longer than the time to perform the test. Management attitudes and lack of understanding can also adversely affect the quality of a second person review for the worse. In the final part of this series, we will look at analyst training and how to establish and maintain an open culture and metrics for monitoring chromatographic analyses.

References

(1) M.E. Newton and R.D. McDowall, *LCGC North Am.* **36**(1), 46–51 (2018).

(2) M.E. Newton and R.D. McDowall, *LCGC North Am.* **36**(4), 270–274 (2018).

(3) M.E. Newton and R.D. McDowall, *LCGC North Am.* **36**(5), 330–335 (2018).

(4) M.E. Newton and R.D. McDowall, *LCGC North Am.* **36**(7), 458–462 (2018).

(5) 21 *CFR* 211 Current Good Manufacturing Practice for Finished Pharmaceutical Products (FDA, Silver Spring, Maryland, 2008).

(6) EudraLex - Volume 4 Good Manufacturing Practice (GMP) Guidelines, Chapter 6 Quality Control. (European Commission, Brussels, Belgium, 2014).

(7) R.D. McDowall, *Data Integrity and Data Governance: Practical Implementation in Regulated Laboratories* (Royal Society of Chemistry, Cambridge, UK, 2018).

(8) U.S. Food and Drug Administration, *Guidance for Industry Data Integrity and Compliance with cGMP* (FDA, Silver Spring, Maryland, 2016).

(9) U.S. Food and Drug Administration, *Warning Letter IDT Australia Limited (Warning Letter 320-18-55)*.(FDA, Silver Spring, Maryland, 2018).

(10) WHO Technical Report Series No.996 Annex 5 Guidance on Good Data and Records Management Practices. (World Health Organization, Geneva, Switzerland, 2016).

(11) C. Burgess and R.D. McDowall, *LCGC Europe* **29**(9), 498–504 (2016).

(12) EudraLex - Volume 4 Good Manufacturing Practice (GMP) Guidelines, Annex 11 Computerised Systems. (European Commission, Brussels, Belgium, 2011).

(13) R.D. McDowall, *Spectroscopy* **32**(11), 24–27 (2017).

(14) R.D. McDowall, *Spectroscopy* **32**(12), 8–12, 28 (2017).

Mark E. Newton is the principal at Heartland QA in Lebanon, Indiana. Direct correspondence to: mark@heartlandQA.com

R.D. McDowall is the director of RD McDowall Limited in the UK. Direct correspondence to: rdmcdowall@btconnect.com

This article first appeared in LCGC North Am. ***36*** *(8), 527–529 (2018).*

Open Culture, Training, and Monitoring Metrics

Mark E. Newton and R.D. McDowall

In the first five parts of this series, we have discussed data integrity throughout the analytical process. In the final installment, we look at three requirements for establishing and supporting data integrity in a regulated laboratory. These are an open culture, data integrity training, and quality and data integrity metrics.

This is the last of six articles on data integrity in a regulated chromatography laboratory. The first article introduced a four-layer data integrity model and then discussed sampling and sample preparation (1), the second focused on preparing the instrument for analysis and acquiring data (2) and the third discussed integration of acquired chromatograms (3). Article four discussed calculation of the reportable result (4) and the fifth one presented second-person review (5).

The Foundation of Data Integrity

A data integrity model was presented in that first article that consisted of four layers: a foundation layer and three levels above it (6,7). The model works like building a house: A firm foundation allows the three levels above it to function correctly. Therefore, for the final part of this series, we look at three topics within the foundation layer that are essential for supporting data integrity throughout the analytical process:

- An open culture
- Training for data integrity
- Metrics to monitor the analytical process and data integrity.

Establishing and Maintaining an Open Culture

Establishing and maintaining an open culture is the hardest part of a data integrity program. You can have all the procedural and technical controls plus training, but if you don't have the open culture and ethos, it will be wasted because management can put pressure on staff to cut corners.

The following sections discuss some of the key elements of an open culture.

Open Culture, Training, and Monitoring Metrics

Leading from the Top

Data integrity comes from the top of the organization. Senior management must ensure that they communicate their requirements for data integrity, and obtain feedback to ensure that their requirements are met. Communication is not a single e-mail to all staff, but is reinforced by including data integrity requirements in everybody's job description and objectives; also, an individual's performance for data integrity, in part, should be linked to pay.

In parts I–V of this series (1–5), we have had a running section "Is Management the Problem?" to discuss the impact management can have on a laboratory's approaches to data integrity. These are additional areas where management must be aware, to ensure that the laboratory staff protect data integrity and don't just pay lip service.

Changing the Mindset

A laboratory must move from a blame culture to a learning organization. This approach is illustrated by a quote from Deming (8):

> "Fear invites wrong figures. Bearers of bad news fare badly. To keep his job, anyone may present to his boss only good news."

There must be the ability to allow staff members to own up if they have made a mistake without the fear of being ridiculed or pointed out as inept. At this point, it is worth quoting from the U.S. Food and Drug Administration's (FDA's) Out of Specification (OOS) guidance on analyst responsibilities (9):

> *"If errors are obvious, such as the spilling of a sample solution or the incomplete transfer of a sample composite, the analyst should immediately document what happened.*
>
> *Analysts should not knowingly continue an analysis they expect to invalidate at a later time for an assignable cause (that is, analyses should not be completed for the sole purpose of seeing what results can be obtained when obvious errors are known)."*

Here is a requirement from the FDA for openness and honesty. The move to a learning organization now allows you to ask why a mistake was made. Can we learn from this and improve and prevent the situation from re-occurring? Following are a few examples of reasons for a mistake:

- A procedure is too complex to follow consistently.
- There is too much pressure to release a batch as production is waiting to ship.
- Missing a turnaround target time has too much influence on data integrity and data quality.

The *GAMP Guide on Records and Data Integrity* details the types of mistakes and their impact (10).

Observing Actual Practices

Closely linked to management leadership is a gemba walk, where managers get out of their offices and see what is happening first hand, rather than filtered through organizational layers. This practice is an opportunity for management to encourage data integrity, and for staff to inform management of problems with processes and systems.

Table 1: Corporate procedures for data integrity

Document Title	Contents of the Document
Data Integrity Policy	• Corporate expectations for data integrity and ethics • Roles and responsibilities of all staff for data integrity • Open culture, expected behavior, and ability to admit mistakes • Raising data integrity issues in confidence • Investigation of data integrity violations
Good Documentation Practices	• Principles and requirements of good documentation practices • Defining raw data and complete data • Documenting paper processes • Documenting hybrid processes: paper and electronic records • Documenting electronic processes: electronic records
Evaluating and Selecting Analytical Instruments	• Process for evaluating, selecting and purchasing new analytical instruments and systems • Laboratory user requirements specification • Scientific evaluation of the instrument • Compliance evaluation of the associated software for regulatory compliance and data integrity gaps

In part V (5), we mentioned that, without investment in laboratory automation and systems, the second-person review now can take longer than the actual analysis, slowing release of product to the market. Management must be made aware of such issues.

Equally so, a gemba walk can be an opportunity or staff to show management where data integrity successes have occurred, say by the elimination of a hybrid system as a result of automation. For more information on an open culture, see the ISPE Cultural Excellence Report (11).

Training for Data Integrity

One of the keys to success, ensuring both data integrity and regulatory compliance, is adequately trained and competent analysts. There are several policies and procedures that we first need to introduce, and then we can discuss how training needs to take place. First, we will consider procedures at a corporate level and second, discuss chromatography laboratory standard operating procedures (SOPs).

There are three high-level policies or procedures shown in **Table I** that we will discuss first along with the approaches for training.

- A Data Integrity Policy lays out the principles for data integrity and ethos within the organization along with the expected behavior of all staff (6,7,10). This document is too important for a read-and-understand approach when training the staff; additionally, such an

approach will not lead to consistency of action. A much better approach is offered by the National Environmental Laboratory Accreditation Conference (NELAC) (12), and outlined in more detail (6,7). There needs to be an introduction to the session by management in which the policy is viewed and explained with examples of both required and prohibited actions. To reinforce the training, copies of the policy and all training materials should be given to each attendee to make their own notes. Because of the importance of this subject, we recommend an assessment at the end with a high pass mark. After the training has been passed, each employee should sign a form declaring that he or she understands the training and the consequences of failing to follow the policy. Staff that fail the assessment should retake the whole of the training and assessment.

- Good Documentation Practices (GDocP) training needs to be undertaken in a similar way to the data integrity policy with a copy of the procedure and the training materials followed by an assessment (6,7). Although most laboratories have a procedure for GDocP, those procedures focus mainly on paper records. This policy needs to be extended to include hybrid systems (including record–signature linking) and electronic systems. The procedure needs to cover what is meant by complete data and raw data (13) in a laboratory.
- Evaluation and Selection of Analytical Instruments and Systems. With the issue of the new version of *USP* <1058> on Analytical Instrument Qualification (14), there is an opportunity to update laboratory procedures to ensure correct specification, evaluation, and selection of new instruments and systems (15). There is little point in assessing and remediating current processes and systems if the laboratory continues to purchase inadequate systems that also require remediation before they are operational. Accepting these inadequate systems increases the use of logbooks, which slows the second-person review, as discussed in the fifth article of this series (5).

Focusing on the chromatography laboratory, there are four main SOPs that impact data integrity, as shown in **Table II**:

- Chromatographic integration
- Calculation and rounding
- Second-person review
- OOS investigations.

Because these SOPs have been covered earlier in this series, we do not propose to discuss them further and readers are referred to the applicable part of this series in Table II.

Data Integrity Metrics

As background for data integrity metrics, Newton and McDowall published an overview on the subject in LCGC Europe (16). This article contains the requirements from the various data integrity guidance documents on quality metrics (17,18). It is worth quoting

Table 2: Procedures for data Integrity in a chromatography laboratory

Document Title	Contents of the Document
Chromatographic Integration	• How to integrate chromatography peaks • Order of injection integration: SSTs, standards, and samples • Analytical procedures when you can and cannot integrate peaks • See part III for the content of this procedure (3)
Calculation and Rounding of Data	• How to round numbers • When to round numbers • See Part IV for the content of this procedure (4)
Second Person Review	• Who can be a second person reviewer • Procedure covers manual, hybrid, and electronic processes • See Part V for the content of this procedure (5)
Out of Specification Investigations	• Trigger for invoking the procedure • Laboratory investigation options • Scientific basic for OOS invalidation • See Part V and the FDA OOS Guidance for the content of this procedure (5,9)

the following note of caution before any metrics are considered (18):

"Caution should be taken when key performance indicators are selected, so as not to inadvertently result in a culture in which data integrity is lower in priority."

Metrics should be collected automatically to prevent bias. When starting to use metrics, keep it simple at first (16). Some key metrics can be used to monitor the calculation process, as described below.

Runs Aborted

Reporting runs that were started, but not concluded, can point toward analysts looking at data during the run, then making the decision to terminate the run to avoid accepting data they believe may be OOS, out of trend (OOT) or out of expectation (OOE). Aborted runs, in a well-controlled GMP environment, should always be viewed with a suspicious eye.

Short Runs

Reporting runs that have fewer than an accepted number of injections (for example, three injections) is a means of detecting analysts who re-inject a sample to obtain a new result that can replace one from a previous injection.

Run Evaluation Sequence

As mentioned in part III of this series (3), there should be a procedural order for processing a chromatography run:

1. evaluation of system suitability
2. evaluation of reference standard acceptability
3. evaluation of method acceptance criteria
4. evaluation of sample results.

It is possible to create reports that ensure this sequence of events is happening, based on time stamps of events. This report can point toward analysts evaluating sample results before other acceptance criteria, then finding means to reject the run, such as manipulating standards or suitability to ensure failure of the run—a type of "testing into compliance."

Recalculated Dataset

Monitoring runs that are calculated more than once has two benefits: It is one means of looking across runs for potential improper activities, but it also can point out methods that are not well configured, and therefore require additional manual intervention. Recalculations and manual integrations not only have data integrity impact, but lab efficiency as well.

Manual Integration

For each analytical method at each site, report the number of peaks automatically integrated and manually integrated. This metric provides insights that lead to more automated integration. For example, Site A automatically integrates 80% of all peaks for method Y, whereas all other sites using the same method automatically integrate only 30% of their peaks. What do analysts at Site A know about this method that permits such a high level of automated integration?

Benchmarking

For each report type, generate a summary report that compares the number of records found by site. This summary report permits comparisons, and reveals sites that have unusually high (or low) activity compared to other sites. For example, a site with twice the number of aborted runs as other sites might lead to a quality assurance inquiry to understand the high number of aborts. Perhaps equipment issues, a fragile method, or poor behaviors are the root of the issue, but the report creates the signal that starts the investigation.

Metrics Governance

For companies with multiple sites of operation, a supervisory layer of metrics should be created to provide a view of metrics reports. At a minimum, this supervisory layer should provide counts for the type and number of reports generated (either visually or on paper) for each site. This provides insight to the question, "Are people using the reports in our operations?" Failure to use reports indicates either a lack of understanding about the reports, or a lack of report effectiveness. In addition to use frequency, the number of investigations and number of issues uncovered should be monitored to assess the effectiveness of metrics. Reports that seldom lead to discovering real issues should be modified or replaced with more effective reports.

Ideas for Metrics

The best ideas for monitoring metrics often come from regulatory enforcement actions (for example, Warning Letter, Notice of Concern, and so forth). The only twist is to read the cited deficiency and ask yourself, "How would we detect this situation in our own operation?" This question will cause you to think about the data patterns that accompany the behavior and then to formulate a query that could detect the data pattern. For example, a firm is cited for manipulating the system clock to falsify timestamps in audit trail records. If this falsification happens, there could be a series of system audit trail entries, one for each clock adjustment. In addition, there will be some frequently written audit trails (such as intersystem messages) where the clock will appear to go backward because of the clock manipulation. So, a query that checks for clock entries that do not continue to increase could flag clock manipulation behavior.

Limitations of Metrics

It is important to remember that all metrics are not created equal; some will prove more effective than others in your operation. In addition, metrics seldom identify a true issue with every reported record in a report. Rather, they highlight suspicious records that require a human to investigate. This investigation requires a time investment, and therefore becomes a limitation on reporting effectiveness. Finally, some real issues will not be detected in a report, such as reanalyzing a sample on a simple instrument (for example, a pH meter), picking the desired outcome and forwarding it to laboratory information management system (LIMS). This data integrity issue will not be detected on any report.

Summary

Over the six parts of this series, we have covered the whole of the analytical process for chromatography. To conclude, we would like to summarize the key points from each article (see **Table III**).

Data integrity in the chromatographic process requires a holistic look at the end-to-end process, identifying places in the process where actions can impact the integrity of the reportable results, then putting controls in place to mitigate the risks. In addition, metric reports must be identified from known issues, to observe the process at a more abstract level, looking for potential signals or trends that deserve closer investigation by qualified personnel.

These actions require the support of senior management, who provide the needed resources for governance and training, and more importantly, who lead by example and regularly inspect the operation to ensure that controls are both used and effective for their purpose.

Table 3: Key learning points from the six-part data integrity series

Topic of the Part	Key Data Integrity Issues
Sampling and sample preparation	• Ensure each sampling plan is scientifically sound and that samples are taken and labeled correctly. • Automate the collection of sampling information. • Automate sampling and sample preparation to reduce dilution and extraction errors.
Preparing a chromatograph and acquiring data	• Consider risks for entry or transfer of factors, weights, or other assay values for calculations. • Limit storage locations of injection results to avoid diversion of data and potential of creating orphan data. • System suitability failures must be scrutinized to rule out the possibility of using suitability failure to eliminate undesirable sample results.
Integrating and interpreting data	• Do not use integration techniques to mask a poor method; instead, fix the method. • All actions for integration, calculation, and reporting of data should be directed from a chromatography SOP. • Sample results should not be integrated until after a run's acceptability is established, to avoid potential issues of testing into compliance.
Calculation of the reportable result	• The order of calculations is important to avoid testing into compliance. • Use CDS or LIMS/ELN for method calculations whenever possible. • Avoid the use of spreadsheets due to their data integrity risks. • Interfaces (human and machine) are potential data integrity issues and their risks must be managed.
Second-person review	• The review must include all raw data necessary to conform to regulations. • Testing data excluded from final result calculations must be included for review. • Paper records—especially logbooks—can make second-person review longer to complete than performing the analytical method. This timing is improved with electronic records.
Training, culture, and metrics	• An open culture is a critical factor to maintain data integrity. • Training must include every person's responsibility to ensure data integrity. • Automated metrics can help identify potential signals or trends that merit additional scrutiny.

References

(1) M.E. Newton and R.D. McDowall, LCGC *North Am.* **36**(1), 46–51 (2018).

(2) M.E. Newton and R.D. McDowall, LCGC *North Am.* **36**(4), 270–274 (2018).

(3) M.E. Newton and R.D. McDowall, LCGC *North Am.* **36**(5), 330–335 (2018).

(4) M.E. Newton and R.D. McDowall, LCGC *North Am.* **36**(7), 458–462 (2018).

(5) M.E. Newton and R.D. McDowall, LCGC *North Am.* **36**(8), 527–531 (2018).

(6) R.D. McDowall, *Validation of Chromatography Data Systems: Ensuring Data Integrity, Meeting Business and Regulatory Requirements* (Royal Society of Chemistry, Cambridge, UK, 2nd Ed., 2017).

(7) R.D. McDowall, *Data Integrity and Data Governance: Practical Implementation in Regulated Laboratories* (Royal Society of Chemistry, Cambridge, UK, 2018).

(8) W.E. Deming, *The New Economics for Industry, Government, Education* (MIT Press, Cambridge, Massachusetts, 2nd Ed., 2000)

(9) U.S. Food and Drug Administration, Guidance for Industry Out of Specification Results (FDA, Rockville, Maryland, 2006).

(10) GAMP Guide Records and Data Integrity (International Society for Pharmaceutical Engineering, Tampa, Florida, 2017).

(11) ISPE Cultural Excellence Report (International Society for Pharmaceutical Engineering, Tampa, Florida, 2017).

(12) NELAC Quality Standard (National Environmental Laboratory Accreditation Conference, Weatherford, Texas, 2003).

(13) R.D. McDowall, *Spectroscopy*, **31**(11), 18-21 (2016).

(14) USP 41 General Chapter <1058> Analytical Instrument Qualification (U.S. Pharmacopeial Convention, Rockville, Maryland, 2018).

(15) R.D.McDowall, *Spectroscopy*, **32**(9), 24-30 (2017).

(16) M.E. Newton and R.D. McDowall, *LCGC Europe*, **30**(12), 679–685 (2017).

(17) WHO Technical Report Series No.996 Annex 5 Guidance on Good Data and Records Management Practices (World Health Organization, Geneva, 2016).

(18) PIC/S PI-041 Draft Good Practices for Data Management and Integrity in Regulated GMP/GDP Environments Pharnaceutical Inspection Convention/Pharmaceutical Inspection Co-Operation Scheme, Geneva, 2016).

Mark E. Newton is the principal at Heartland QA in Lebanon, Indiana. Direct correspondence to: mark@heartlandQA.com

R.D. McDowall is the director of RD McDowall Limited in the UK. Direct correspondence to: rdmcdowall@btconnect.com

This article first appeared in LCGC North Am. ***36*** *(9) (2018).*

Agilent CrossLab
From Insight to Outcome

Move Your Analytical Instrument Qualification to Agilent

At a time when laboratories are focusing on reducing costs, increasing productivity and maximizing return on investment, they need to be ready to address fundamental questions about the compliance of their Analytical Instrument Qualification (AIQ) during laboratory audits and inspections.

The Agilent Automated Compliance Engine is designed to simplify compliance with data integrity requirements, while providing a harmonized and cost-effective approach which is not limited to a particular instrument manufacturer or software.

Move to Agilent today! Visit www.agilent.com/chem/qualification

Agilent