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Data Integrity Tips for Regulated Laboratories, Part 1

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Nightmare on Lab Street—Are You Haunted by Hybrid Systems?

R.D. McDowall

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Hybrid CDS applications are pervasive in analytical laboratories. However, they are the worst possible solution because you must synchronize and manage two incompatible data formats: paper printouts and electronic records. We discuss why hybrid systems are the wrong approach and what you can do to remove this specter.

Welcome to a new decade, and a new series of "Data Integrity Focus" articles for your reading pleasure. Let me start by being brutally honest: Hybrid systems are the worst possible solution to have in any regulated or unregulated laboratory. Having made such a bold statement, we will discuss what hybrid systems are and why I have come to that conclusion. I'll give you some free consulting advice: Don't use them! As most of you will ignore this advice, I'll also look at a possible interim solution that could help reduce the volume of paper printed, and make the second person-review of chromatography data simpler and easier.

What is a Hybrid System?

Before we begin to discuss the disadvantages of a hybrid system (and there are no advantages), we had better define what a hybrid system is. The best definition of a hybrid system or approach is found in the WHO guidance on good data management practices:

> *This refers to the use of a computerized system in which there is a combination of original electronic records and paper records that comprise the total record set that should be reviewed and retained (1).*

It then explains in more detail the requirements to link and synchronize the two incompatible media:

> *An example of a hybrid approach is where laboratory analysts use computerized instrument systems that create original electronic records and then print a summary of the results. The hybrid approach requires a secure link between all record types, including paper and electronic, throughout the records retention period. Where hybrid approaches are used, appropriate controls for electronic documents, such as templates, forms and master documents, that may be printed, should be available (1).*

The main points that we can draw out from this definition are:

- A hybrid system has both electronic records and printouts. However, note the phrase "original electronic records." This is important, because a computerized system, in our case a chromatography data system (CDS), must acquire or create and process electronic records first before they can be printed out; hence they are original e-records that we will discuss later in this article.
- What is missing from the WHO definition is that the analyst and second-person reviewer will sign on the paper printouts as either the performer and reviewer for each analysis, as required by U.S. Food and Drug Administration (FDA) and European Union (EU) regulations (2,3).
- Following on from the last point, there needs to be as secure link between the handwritten signatures on the paper printout with the source electronic records in the CDS.
- There should be, but usually isn't, controlled copy printing from the system (for example, each printout is labelled copy 1, copy 2, etc.) Otherwise, how sure can we be that the analysis is original, and not a result of testing or integrating into compliance? Alternatively, if there is a second printing, there is a scientifically sound reason for this and copy 1 is retained as part of the complete data for the analysis (2).

Why All the Fuss About Hybrid Systems?

The problem with hybrid systems can be traced back 15 years to the Able Laboratories fraud case. Able was a generic pharmaceutical company based in New Jersey that took a rather unusual approach to analysis, as shown by citation 5 of the Form 483 given at the end of a for-cause inspection:

> *The substitution of data was performed by cutting and pasting*

of chromatograms, substituting vials, changing sample weights and changing processing methods… Sample weights were changed by the analyst until a passing result was obtained (4).

The worrying point for the FDA was that they had inspected the company seven times without identifying any falsification of data. The problem was that the inspectors only focused on paper printouts, and never looked at CDS electronic records and audit trail entries—that is, until a whistle blower called the local field office, and the rest is history. This case has resulted in two updates of Compliance Program Guide 7346.832 for Pre Approval Inspections (PAIs), with increased focus on data integrity in both versions (5–7).

Hybrid Records for a CDS

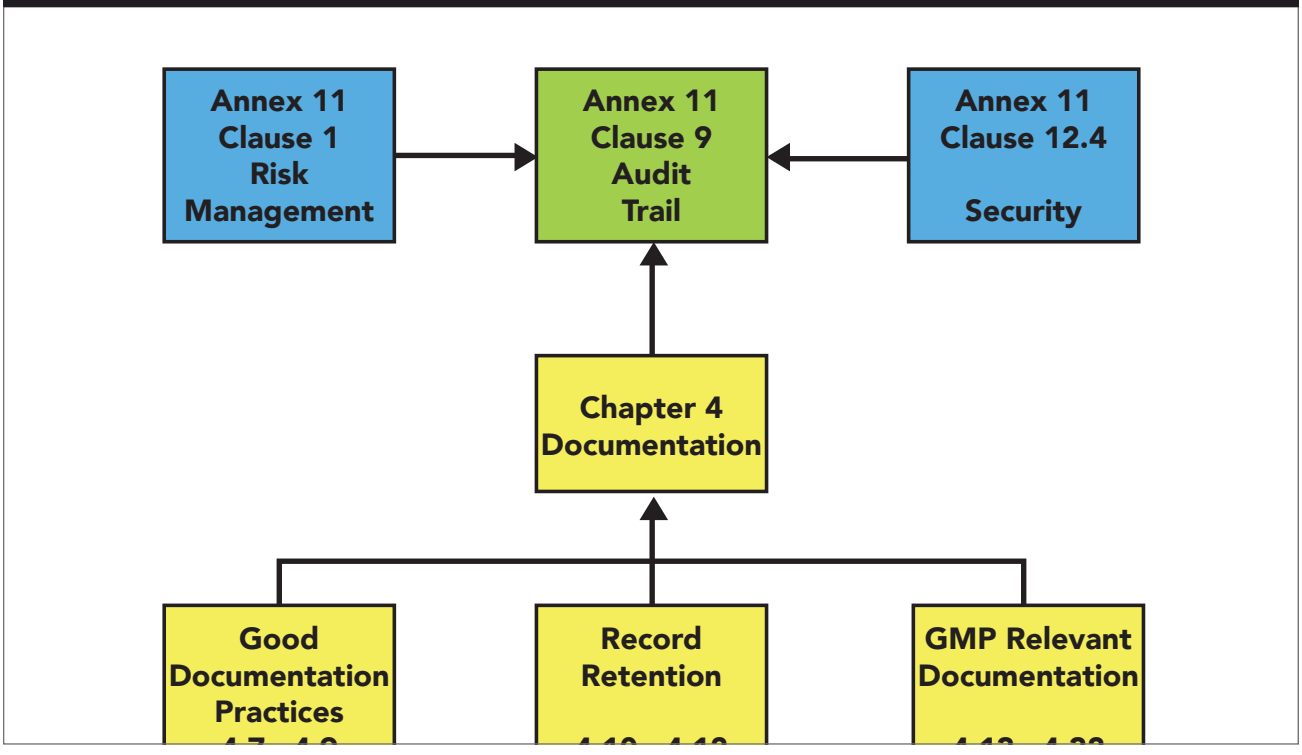
Having established that a hybrid system consists of both electronic records and signed paper printouts, what does this look like for a CDS? Shown in **Figure 1** is a hybrid CDS controlling a single instrument. This system can be either a standalone or a networked system, because the principles for a hybrid system are the same regardless of the architecture. The figure is color-coded as follows:

- Yellow indicates that these are paper records that are either generated during the course of analysis or printouts from the CDS application.
- Green is the main flow of data within the CDS from acquiring each data file, processing or integrating peaks, followed by calculating individual aliquot results, and, finally, the reportable value.
- Blue represents the metadata that put the context around the green data files of an analytical run including the audit trail entries.

Seen in **Figure 1**, the complete record set of a hybrid CDS consists of:

1. The electronic records within the data system, including the chromatographic data files and the contextual metadata used to acquire them (sequence file, instrument control file, and acquisition method), then process them to calculate the reportable result (processing method, post run calculations, sequence file containing standard purity and water content, dilutions, and other factors that used to calculate the individual and reportable results.
2. Paper records for sampling and sample preparation, as well as the paper printouts from the CDS—this may vary from a summary report to a summary plus all chromatograms. The CDS printout is hand signed by the performer of the test and the reviewer of the whole record set from sampling to final result.

Figure 1: A hybrid chromatography data system.



3. Entries in the instrument maintenance and use log, that we will discuss later in this article.

You can see that there are two incompatible record formats to manage. It is this combination of electronic records and paper printouts that must be synchronized from creation to destruction throughout the record retention period that makes it the worst situation to be in. Moreover, the WHO guidance goes further and makes the statement that if you look only at paper printouts, poor data management issues and falsification may be missed during the second-person review:

> *Data integrity risks may occur when people choose to rely solely upon paper printouts or PDF reports from computerized systems without meeting applicable regulatory expectations for original records. Original records should be reviewed—this includes electronic records. If the reviewer only reviews the subset of data provided as a printout or PDF, risks may go undetected and harm may occur (1).*

From the perspective of the WHO, it is not looking good for hybrid systems. This statement is also déjà vu of the Able Laboratories fraud case discussed

earlier. However, hybrids are very common in many laboratories. But can things get any worse?

In some laboratories, yes, they can, as we will shall see now.

You Cannot Be Serious!

Figure 1 shows the most optimistic version of a hybrid system, where all system suitability test (SST) and sample calculations are performed within the CDS application. Here, all the electronic records for the analysis are contained in a single computerized system, and there is only a single printout from an analytical run.

But...there is always the siren call of the spreadsheet, a ubiquitous application that is easy to use for those lazy sloths that can't be bothered to read the CDS instruction manual. Furthermore, despite all the suppliers of CDS applications incorporating a wide range of SST parameters and calibration curve models into their software (with the added advantage that you don't have to print and retype the peak areas into the spreadsheet), the laboratory develops a spreadsheet template to do the same job. I have often wondered whether chromatographers are masochists, and here is the proof.

Now, I suggest you stand back and look at the specter you have created, that which will haunt you unless you change. Instead of the relatively manageable process shown in **Figure 1**, we now have the stupid (please feel free to insert your own alternative adjective here) situation, where we have made the process more complex, more error prone, with increased record vulnerability, and with not one but two hybrid systems! With transcription error checking between the two systems added for free, besides. I could not write fiction like this.

Chromatographic Data Are Dynamic

Implicit in **Figure 1** is the fact that chromatographic data are dynamic and not static records. As you can see, post-acquisition there is automatic and manual integration (if the latter is allowed) to process the data, followed by post integration calculations such as calibration and adjustment by factors such as purity and dilutions. What is the difference between the dynamic and static data? The best description is found in the FDA Guidance on Data Integrity and cGMP Compliance, where an edited version is presented below:

> Q1d. How does FDA use the terms "static" and "dynamic" as they relate to record formats?
>
> *…static is used to indicate a fixed-data record such as a paper record or an electronic image, and dynamic means that the record format allows interaction between the user and*

the record content. For example, a dynamic chromatographic record may allow the user to change the baseline and reprocess chromatographic data so that the resulting peaks may appear smaller or larger...(8).

There you have it: Chromatographic data are dynamic records. As such, CDS and the data they contain are firmly in the sights of regulatory authorities worldwide, as slight changes in baseline positioning in a sample chromatogram can turn a failing result into a passing one. These changes can be hidden, if paper is the focus of an audit or inspection.

We will now see what other regulations and guidance documents say about hybrid systems.

EU GMP Chapter 4 Principle

EU GMP Chapter 4 on Documentation includes the following statements concerning hybrid systems:

Many documents (instructions and/or records) may exist in hybrid forms, i.e. some elements as electronic and others as paper based.

Relationships and control measures for…records need to be stated for… hybrid…systems.

Appropriate controls should be in place to ensure the integrity of the record throughout the retention period (9).

Here is the requirement to identify both paper printouts and underlying electronic records for each hybrid system, and to protect both types of records throughout the record retention period. However, the identification of the all records for each computerized system is not always documented in many laboratories, until a data integrity assessment of the system is undertaken.

WHO Good Records Management Guidance

Let me return briefly and brutally to the WHO guidance for the view on hybrid systems. Below are two statements that are about as far as a regulator can go without saying, "Don't use these systems!":

The use of hybrid systems is discouraged, but where legacy systems are awaiting replacement, mitigating controls should be in place.

Replacement of hybrid systems should be a priority (1).

How should you interpret "discouraged?" Don't use hybrid systems would be a good first try.

Record–Signature Linking Requirements

The requirements for linking handwritten signatures on paper to the underlying electronic records in a CDS are found in the 21 CFR 11 regulations

for electronic records and electronic signatures, specifically in 21 *CFR* 11.70:

> *Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means (10).*

Now, the problem is that many people think that 21 *CFR* 11 regulations only apply to electronic signatures as applied to electronic records. However, it explicitly states above that handwritten signatures executed to electronic records shall (please interpret this as must) be linked to their respective electronic records. Therefore, the paper printout must identify not only the key data files that have been used to generate the printout or report, but also the key contextual metadata involved in the generation and processing of the data. Not all contextual metadata needs to be identified on the report (typically, these are the audit trail entries) but if the analytical run is accessed in the CDS, then the remaining metadata need to be easily accessible. This record signature linking is a technical control that is the responsibility of the application supplier. However, the laboratory does not escape responsibility, as there should be a file naming convention for contextual metadata, such as "chromatographic methods" and "processing methods,: and so on.

Why Can't I Use Paper as My Original Records?

Rather than answer this question, I'll get my North American advertising agency to answer it on my behalf. Question 10 in the FDA data integrity guidance asks, "Is it acceptable to retain paper printouts or static records instead of original electronic records from stand-alone computerized laboratory instruments, such as an FT-IR instrument? (8)"

The simple answer is no. However, a better discussion on this issue and focused on chromatographic data can be found on the FDA web site under the snappy title of "Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance—Records and Reports (11)." Here, Question 3 asks: "How do the Part 11 regulations and 'predicate rule requirements' (in 21 *CFR* Part 211) apply to the electronic records created by computerized laboratory systems and the associated printed chromatograms that are used in drug manufacturing and testing?"

The FDA starts to answer the question by stating that some people misinterpret the Part 11 Scope and Application guidance (12) (lines 164 to 171) to mean that, in all cases, paper printouts of

electronic records satisfy predicate rule requirements in 21 *CFR* 211. This is not the case, as the guidance also states:

> *…persons must comply with applicable predicate rules, and records that are required to be maintained or submitted must remain secure and reliable in accordance with the predicate rules (12).*

The two applicable GMP predicate rules cited are 21 *CFR* 211.180(d) and 21 *CFR* 211.68(b) (2). The former requires records to be retained either as original records or true copies, and the latter states backup data are exact and complete. The FDA view is that:

> *The printed paper copy of the chromatogram would not be considered a "true copy" of the entire electronic raw data used to create that chromatogram, as required by 21* CFR *211.180(d). The printed chromatogram would also not be considered an "exact and complete" copy of the electronic raw data used to create the chromatogram, as required by 21* CFR *211.68. The chromatogram does not generally include, for example, the injection sequence, instrument method, integration method, or the audit trail, of which all were used to create the chromatogram or are associated with its validity.*
>
> *Therefore, the printed chromatograms used in drug manufacturing and testing do not satisfy the predicate rule requirements in 21* CFR *Part 211. The electronic records created by the computerized laboratory systems must be maintained under these requirements (11).*

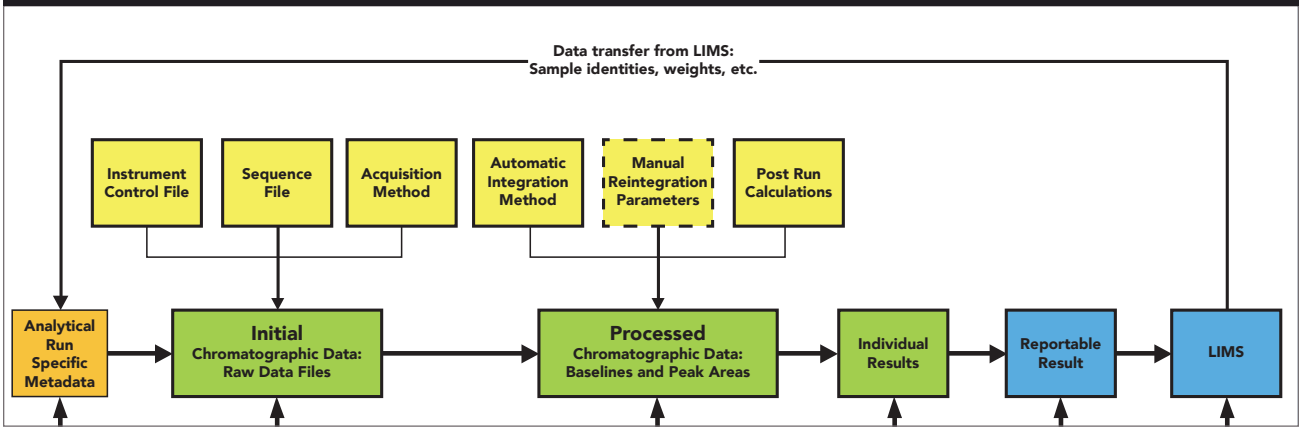
This principle applies to all GMP records: Do not ignore or delete e-records and only rely on paper printouts. This applies to CDS and spectrometry systems as well as spreadsheets. Therefore, you should now understand the rationale for my comment earlier in this article that a CDS and spreadsheet combination results in two hybrid systems.

Can I Reduce Paper with a Hybrid System?

There is a suggested approach for reduction of paper printouts from hybrid systems that can be found in the WHO data integrity guidance in the Appendix under "Special Risk Considerations for Attributable" (1). A prerequisite is that there needs to be adequate security and backup for the system. As noted earlier, a hybrid approach is likely to be more burdensome than an electronic workflow with electronic signatures. An approach is shown in **Figure 2** and described below:

- Create a controlled blank form that is linked to the SOP for the CDS analysis and data review. There

Figure 2: A suggested approach to reduce paper output from hybrid systems [process is from reference (1), figure is from reference (3)].



needs to be sufficient space for the performer, reviewer, or approver of the analysis to enter the records created or used, as well as hand sign the form

- As the performer executes the analysis, the data files created and the associated contextual metadata used are recorded on the form, along with the location of where the records are stored (for example, in a directory or project). When complete, the performer signs the form to link his or her signature to the CDS electronic records generated and used in the analysis.
- The form passes to the reviewer, who now has a list of electronic records to review, along with applicable audit trail entries. The review is conducted electronically on screen; no chromatograms are printed. The reviewer checks the record set to ensure work has been conducted correctly, and that all calculations are correct. In addition, if technical controls are not in place to control data storage, locations where data could be stored to mask unofficial testing or searches to identify short or aborted sequences should be conducted by the reviewer. When complete, the reviewer will sign for completing the review.
- If required by local procedures, the controlled form is passed to an approver. Note that this is not a regulatory requirement; only two people are required by 21 *CFR* 211.194(a) (2).

This reduces the volume of paper printed by the system to either the controlled blank form and possibly a simple report of the results. Reiterating the points above, all review is carried out on screen which makes the backup and security

of the electronic records in the CDS paramount. The benefit of this approach is that it makes long term retention simpler and easier. However, we have forgotten an essential element in both analysis and review: the instrument log book, as shown in **Figure 1**.

The Trilogy of Electronic Records, Paper, and Log Book

When using a hybrid system, there are three essential elements to ensure data integrity that are shown in **Figure 1**.

1. The electronic record set for the analysis: the chromatography data files and the associated contextual metadata, such as sequence file, instrument control method, sequence file, processing method and audit trail entries.
2. Paper records comprising sample preparation worksheets, including balance records for sample weights and printouts from the CDS after interpretation and calculation of the reportable result(s), or the controlled worksheet described above.
3. Instrument log book entries for the analytical run

The instrument log book is an essential component for ensuring data integrity. Log books should record the maintenance, use, calibration, and repair of a chromatograph, as required by 21 *CFR* 211.182 and EU GMP Chapter 4.31 (2,9). However, where technical controls are either not available or use of them is not feasible (such as where logging off would stop the analysis), the instrument log should record actions of users who interact with the system but are not logged in. This is acknowledged in both the WHO and PIC/S guidance documents (1,14), with the key section of the PIC/S document stating:

> *some computerized systems support only a single user login ...Where no suitable alternative computerized system is available, equivalent control may be provided by third party software, or a paper-based method of providing traceability (with version control). The suitability of alternative systems should be justified and documented. Increased data review is likely to be required for hybrid systems (14).*

The additional effort and time for the review is justified, as it is a procedural control that is error prone rather than a technical control that is validated and enforced by the CDS application software. For those that would like to go into more detail on this topic, I have written more about the role of an instrument log book in a "Focus on Quality" column in *Spectroscopy* (15). Furthermore, the use of an instrument log book in lieu of an effective audit trail will slow the second-person review process, as noted by Newton

& McDowall (16), which is yet another reason for not using hybrid systems.

The Last Word

Ideally, hybrid chromatography data systems should be reconfigured and revalidated to work electronically with electronic signatures. The principles for this design should be:

- Electronic data should be captured at source.
- All work should be done electronically, with all calculations performed within the CDS and report being electronically signed
- Ideally, sample weights and analysis identities should be downloaded from a LIMS or equivalent application. As this process is validated, the only transcription error checks are for manually entered data.
- Transfer of results to a LIMS or similar application should only be performed by a validated and automatic transfer.
- Know where the data are stored, so that electronic records can be retrieved quickly when required (ideally, this should be on a secure and resilient drive on the network that is backed up regularly by the IT function).

The best approach is to have a CDS architecture, even for a single chromatograph, that has the following attributes:

- networked solution for record security and backup database to manage records.
- For more information on this topic, please read the four-part series on an ideal CDS for regulated laboratories (17–20).

Summary

We have looked at why hybrid systems are the worst possible solution for a regulated laboratory, because there are two incompatible record formats to manage. Focusing on just paper records means that poor data management practices or falsification may be missed, and therefore it takes longer to review hybrid records, because both sets of records plus the instrument log need to be reviewed. If a CDS lacks full audit trail functionality, then a paper record of activities must be maintained in a log book.

In the next article, we will look at audit trail review systems.

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

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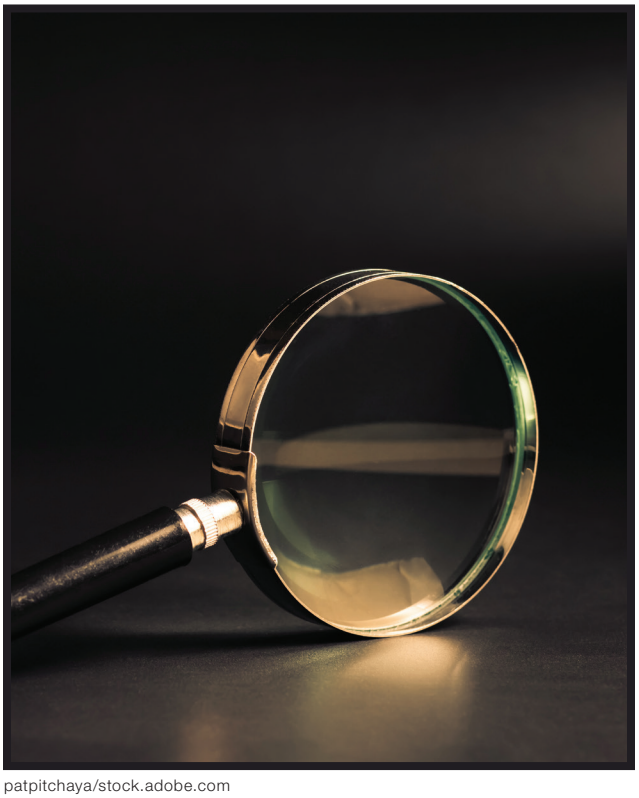

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The Why, What, and How of CDS Audit Trail Review

R.D. McDowall

Audit trail review is a key component of the second person review of chromatographic analysis for compliance with regulations, procedures, and analytical science. We focus on what the review of audit trail entries means, and how to review by exception if the CDS has appropriate technical controls.

Examination of audit trail entries for an analysis is a key part of the second person review. It is over 20 years since EU GMP Annex 11 and 21 *CFR* 11 required audit trails in regulated applications, including the chromatography data system (CDS). What do the regulations say about review of audit trails? How can we speed up the review process? What is review by exception? How can we use this to save review time?

Where It All Began

All those lucky chromatographers who must review CDS audit trails have Able Laboratories to thank for the drudge of ensuring that the analysis has been performed correctly. As citation 1 of the Able Laboratories 483 Observation states:

> *...The Quality Unit failed to: review electronic data as part of batch release, review computer audit trails in the <Redacted> Data Acquisition System, and provide adequate training to analytical chemists (1).*

Here we have the first regulatory citation for failure to review audit trails. However, audit trails, however rudimentary, have been included in major laboratory informatics applications such as laboratory information management system (LIMS) since the 1980s. The problem was that there was little agreement on what was required from a regulatory perspective.

Four Eyes Principle and Second Person Review

The generation of sound analytical results is based on the established "four eyes" principle; one person to perform the chromatographic analysis, and a second person to review the data to show that the work has been performed correctly and that no mistakes have been made. The involvement of a second person is to look with a fresh pair of eyes for anything that the analyst may be overlooked. Now, with the emphasis on data integrity, the second person review has been expanded to check that work has not been falsified, and must include review of the CDS audit trail entries.

The scope of the review must cover the whole of the analytical process: from sampling to the calculation of the reportable result, however we will only consider the audit trail review here. The terms performer and reviewer are stated in 21 *CFR* 211.194(a) (2). I will use the term "reviewer" or "second person reviewer" to indicate the one individual who conducts the checks to ensure that work has been performed correctly, and all data and records have been collected. The reviewer will use a general second person review standard operating procedure (SOP) to control their work, and will, in all probability, have a linked work instruction for each different CDS audit trail to be reviewed (unless you have standardized on a single CDS). Ideally, the CDS can support the audit trail review process with software functions (technical controls) to make it quick and efficient, as we shall discuss later.

What is an Audit Trail?

Before we can review audit trail entries, we need to define what and audit trail is, and then understand the regulations surrounding it and the review process. The simplest definition is found in the 2018 FDA guidance on Data Integrity and cGMP, where question 1c asks, "What is an audit trail?"

> *...audit trail means a secure, computer-generated, time-stamped electronic record that allows for reconstruction of the course of events relating to the creation, modification, or deletion of an electronic record. For example, the audit trail for an HPLC run should include the user name, date/time of the run, the integration parameters used, and details of a reprocessing, if any. Documentation should include change justification for the reprocessing.*
>
> *Audit trails include those that track creation, modification, or deletion of data (such as processing parameters and results) and those that track actions at the record or system level (such as attempts to access the system or rename or delete a file)...(3).*

How did we get here?

Audit Trail Regulations

21 *CFR* 11 (Electronic Records and Electronic Signatures) regulations has clause 11.10(e) that requires:

> *Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records.*
>
> *Record changes shall not obscure previously recorded information.*
>
> *Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying (4)*

See where the definition of audit trail comes from in the FDA data integrity guidance? Straight out of the Part 11 regulation. However, life is not always simple, and Part 11 is no exception.

Interpretation of Part 11 by the Predicate Rule

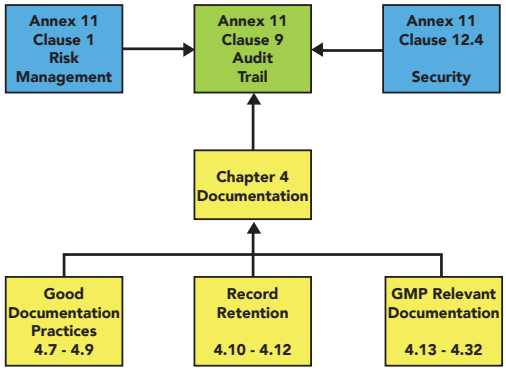
Part 11 only defines the requirements for electronic records and electronic signatures, as that is the role of the predicate file. In our case, the applicable FDA predicate rule is either Good Laboratory Practice (GLP or 21 *CFR* 58) or Good Manufacturing Practice (GMP or 21 *CFR* 211), and you have to interpret these regulations for a complete understanding of FDA regulations for audit trails. For example, there are differences between the two predicate rules. GLP requires a reason for data change in 21 *CFR* 58.130(e) (5), but GMP does not (2). However, it would be a foolish quality control (QC) laboratory that did not implement a reason for change in today's data integrity environment.

This now brings up to 2005, and the Able Laboratories case. How did the FDA cite Able for failure to review audit trail entries? Enter the GMP predicate rule, and specifically 21 *CFR* 211.194(a) for laboratory records. There are two specific requirements:

> *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: (1–7) ...*
>
> *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 (2).*

Although this regulation has been effective since 1978, only since 2005 has the FDA interpreted it to include review of audit trails since the Able Laboratories fraud case. Now we see that when a CDS is involved, a key component of the

Figure 1: Key clauses of EU GMP Annex 11 and interaction with EU GMP Chapter 4 on documentation.



second person review is to review audit trail entries.

Woah!

For a networked CDS there will be thousands of audit trail entries – must I review all of them? To give a rational answer to this, we have to move to Europe, and the update of EU GMP Annex 11 in 2011, to see how regulators have coped post Able with data integrity and any possible data falsification.

Update of EU GMP Annex 11

In 2011, the update of Annex 11 was issued (6). Before we discuss the specific requirements for audit trail in the new version, it is important to understand that the full interpretation of Annex 11 requires an understanding of EU GMP Chapter 4 on Documentation (7). The updates of both these regulations were issued at the same time. **Figure 1** shows the key sections of Annex 11 and Chapter 4 that are pertinent to our audit trail discussion.

Let us work through **Figure 1** to understand the most recent regulations for audit trails and their review. First, there is the Chapter 4 requirement for Good Documentation Practices (GDocP) in section 4.7–4.9 (8), this was discussed in one of last year's Data Integrity Focus articles (9), and will not be repeated here. However, the interpretation of these GDocP requirements on audit trail entries is very relevant, therefore all audit trail entries must be:

- Legible and understandable
- The old and new value for a change must be recorded, along with who made the change
- A reason for changing data is required for all modifications and deletions
- Entries must be date and time stamped. The format of this must be unambiguous, and may also require the time zone, especially for multinational companies.
- Audit trails need to be associated with the activities supported, and it must be possible to search the entries for specific events
- Audit trails must be secure from change
- Audit trails must be retained and

be readable for the record retention period (defined in sections 4.10 to 4.12), and this is at least five years after release of the batch by a qualified person.

This interpretation comes only from the requirements of GDocP and records retention sections in Chapter 4 (7). We now turn to see what the audit trail requirements are in Annex 11.

Annex 11 Requirements for Audit Trail

The updated version of Annex 11 has the following requirements for audit trail documented in clause 9:

> *Consideration should be given, based on a risk assessment, to building into the system the creation of a record of all GMP-relevant changes and deletions (a system generated "audit trail").*
>
> *For change or deletion of GMP-relevant data the reason should be documented.*
>
> *Audit trails need to be available and convertible to a generally intelligible form and regularly reviewed (6).*

Normally, the requirements are presented as a single paragraph, but, for the purposes of this discussion, I have broken these requirements into sentences and clauses. First and foremost, an audit trail is not mandatory, as the phrasing is "consideration … based on a risk assessment…". Before you all rush to turn your CDS audit trails off, please consider the following issues:

- There are many regulatory citations for CDS with audit trails either not turned on, or turned off and then on, to hide falsification activities
- In the absence of an audit trail, Clause 12.4 requires that management systems for data and for documents should be designed to record the identity of operators entering, changing, confirming, or deleting data, including date and time (6).

Therefore, we will not be conducting a risk assessment to justify not having an audit trail, as you will have to comply with clause 12.4. The next is that the audit trail focuses on GMP-relevant changes and deletions, unlike a Part 11 audit trail that also includes creation of the records in 11.10(e) (4). You have to interpret what are GMP-relevant changes and deletions.

Any change to data requires a reason for change, as this is consistent with the GDocP requirements of Chapter 4 (7). This can be implemented either by a drop-down list of context sensitive options to save typing, or by free text. Personally, I prefer the default reasons for change, as this ensures consistency. This option can take time to implement, but the basic functionality must be validated.

Table I: What an audit trail is and is not

AN AUDIT TRAIL IS	AN AUDIT TRAIL IS NOT
• Generated automatically • Secure and linked to a trusted time source • Built with a GMP application (Ideally with a database) • Focused on GMP data generation, modification, and deletion • Can allow an authorized user to enter a reason for change (free text or default entry)	• A text file that is unsecured • Built into a data file as the file cannot monitor its own deletion • A repository for anything to do with the system • A system log • An operating system event log

However, when the CDS is operational, it is best controlled by procedure for adding reasons for change (10).

There is the requirement for audit trails to be available in a generally intelligible form, this refers back to the requirements for GDocP discussed above, but also the need for audit trail entries to be easy to understand and follow.

Finally, the three words that come directly from Able Laboratories: "And regularly reviewed." This is the first, and currently only, explicit regulatory requirement to review audit trail entries, but interpretation always causes much debate and discussion. We shall discuss frequency of review later in this article.

What is An Audit Trail?

Now we have presented and discussed the three main regulations issued over the past 20–30 years for computerized system audit trails, which should be straightforward to interpret in practice.

But, no. We still lack adequate audit trails, or even the existence of an audit trail in many laboratory informatics systems as evidenced in a review of infrared spectroscopy software citations by Smith and McDowall in Spectroscopy (11). Therefore, we need to briefly discuss what is an audit trail, and this is presented in **Table I**.

From all of the regulations, we can show what an audit trail is and is not in **Table I**:

The key requirement is that an audit trail is an integral function in any CDS or any laboratory informatics application. As such, it cannot be bolted on as an afterthought of system design. To be encompassing and effective, the foundation of any audit trail in any application must be a database. The debate between a single audit trail containing all entries versus one for system related entries and one associated with data is outside the scope of this article.

What Are GMP-Relevant Changes?

For an effective and efficient review of audit trail entries, it is essential to understand what the phrase "GMP relevant changes and deletions" in Annex 11 means in practice. As the laboratory

Table II: Identifying some GMP relevant data changes.

GMP Relevant Changes in an Audit Trail	General Audit Trail Entries
• Change batch number of sample	• Logon or logoff by a user
• Move a sample in an injection sequence	• User locks their account
• Modify a sample weight	• Administrator unlocks user account
• Abort a sequence	• Create a new user
• User manually integrates a peek	• Administrator archives an analysis project
• User electronically signs an analysis report	• Change application configuration setting

has configured and validated all laboratory user roles without deletion privileges, a reviewer will not be looking for any deletion entries, will they? That leaves us with just GMP relevant changes, **Table II** lists some audit trail entries that could be found within the audit trails of most, if not all, CDS applications. They are divided into general entries in the right-hand column and GMP relevant changes in the left one.

Let us take the entries in the right-hand column and discuss them first. Here we have logon, logoff, and failed logons, as well as creating an account and unlocking an account by an administrator. Are these GMP relevant changes? Your answer should be an unequivocal "no," as no data have been changed. Equally so, are the archiving of an analyst's project and changing a configuration setting of the application? At this point, there are probably wails of anguish coming from the direction of the quality assurance (QA) department. Let me be very clear here: These last entries are not part of a second person review process. But they will be covered by a QA led data integrity audit to ensure that these actions have the correct authorization, and have followed the appropriate procedure. The entries in the left-hand column of **Table II** are GMP relevant, and must be reviewed during a second person review of any analysis.

However, if you only have a single audit trail covering the whole system, this can present problems, as entries for all analyses, all user logon and logoffs,or any configuration changes can be found in one huge dustbin. To identify GMP relevant changes for the specific analysis that you are going to review needs good search routines.

Risk Management of Audit Trail Review

Next to discuss is a very important clause in Annex 11 that has a major impact on our discussion. Clause 1 states that risk management should be applied throughout the lifecycle… taking into account patient safety, data integrity and product quality (6). Risk management applies not just in the validation of the system, but also during operation of the CDS. Unsurprisingly, this should include

audit trail review, but it often does not. Therefore, we need to consider how we can use risk management to reduce our work reviewing audit trail entries. Of necessity, this approach includes utilizing any technical controls that can be implemented in the CDS application to reduce the amount and number of entries to review.

- Can a user delete data? If all user roles can be configured so that no user has delete privileges, then why should a reviewer look for deletion? To achieve this, there must be a record of how each user role is configured and this must be tested in the system validation. Checks will be performed during data integrity audits that these controls remain in place but, reiterating points made above, do not have to be performed during second person review.
- Can locations where chromatographic data are stored be changed by an analyst? If locations for data storage are controlled by the administrator, and these cannot be changed by a user, then the reviewer need not look at locations for unofficial testing. The procedure and specifications must also be included in the CDS validation.
- Activate the CDS technical controls for audit trail review. Understand and implement any technical controls in your CDS software, such as how does the application highlight SST results not meeting acceptance criteria, files that have been manually integrated, changes to sample weights, purity factors, calculations, etc.?
- Is there an effective audit trail search function? This is to look for activities such as short injection sequences, repeated sequences, or aborted runs as possible poor data management practices.
- Does the system have a function to document audit trail review, or must this be done by procedure? If there is an audit trail review button, then this must be specified in the system User Requirements Specification and be validated. Otherwise, control of audit trail review will involve an SOP.
- Evaluate review by exception. If there are adequate technical controls that identify changes to data (you will not have enabled delete options), and these have been validated, then you can consider audit trail review by exception. This works when there are no data modifications identified by the technical controls monitoring the audit trail. We will discuss this later.

Who Should Review Audit Trail Entries?

One of the main discussion points in

training courses that I have participated in is who should be responsible for reviewing audit trail entries. Answers have varied from analytical development/QC, QA, or even (horror of horrors) IT! How can people and organizations get this so wrong? Audit trail review as part of second person review is a laboratory function. The rationale for my view? It's in the regulations, specifically 21 *CFR* 211.194(a)(2), and EU GMP Chapter 6.17 vii (12).

Recent guidance documents have reinforced this. The FDA's approach in Question 7 of their data integrity guidance (3) is that the people responsible for record review under CGMP should review the audit trails that capture changes to data associated with the record as they review the rest of the record (for example, 211.194(a)(8) [2]). Similarly, PIC/S PI-041 guidance in section 9.5 states that audit trails for each batch should be independently reviewed with all other records related to the batch and prior to the batch's release, so as to ensure that critical data and changes to it are acceptable .. and performed by the originating department, which is the laboratory (13). QA, please note! Your department can verify the effectiveness of the review during data integrity audits or investigations (13–15).

How Regular is a Regular Review?

This is another question with a multitude of wrong answers! Let's see what is discussed in the data integrity guidance documents. FDA's view, stated in question 8 of the 2018 guidance, (3) is that if audit trail review is mandated in 21 *CFR* 211, then this is the review frequency. If the interval is not specified, then determine this according to a risk assessment (a lovely get out of jail excuse!) based on knowledge of the process and the functions of the CDS application, and also include evaluation of data criticality, control mechanisms, and impact on product quality, to ensure that CGMP requirements are met, appropriate controls are implemented, and the reliability of the review is proven (3).

To help you let you understand this, let us move from the vague to the specific, and give laboratory examples. What audit trail review would you conduct for:

- Method development: As method development is seen as outside of GMP, there is no need for a review of audit trail entries. This may be so as there is no mention of method development in ICH Q2(R1) (16). However, this is the critical foundation of a robust analytical procedure, and times are changing, as the analytical world is going to a lifecycle methodology with the publication of a draft USP <1220>, a revision of ICH Q2(R1) in the works. This will be the subject of the next "Data Integrity Focus" article.

"When it comes to on-screen review, it is important that the reviewer has one and preferably two large high-resolution screens."

- Method validation: Audit trail review of the work must be performed before release of the report, but my preference would be at the completion of each experiment to ensure that integrity and quality of the data before the whole validation data become too large.
- Batch release: As discussed earlier, this is mandated by GMP regulations, and therefore must be done before signing of each chromatographic test by the reviewer.
- Stability testing: Similar to batch release, it is important to review audit trail entries after each pull of samples rather than wait for the whole stability study to finish. This is because there are requirements to inform regulatory authorities if an out of specification (OOS) result is obtained.

Performing the Audit Trail Review

Now we can get down to describing how to perform an actual review of audit trail entries. Remember that an audit trail review is only a portion of the overall second person review that starts with sampling and finishes with the calculation of the reportable result. In this section, we will focus on the CDS audit trail review for one analytical run. In this discussion, the technical controls presented earlier are in place and validated to make the review process easier, and there is a procedure in place for review by exception.

First up, do we review audit trail entries on screen, or do we print them out? For those readers that selected the latter option, please write a letter of resignation immediately and reserve a bed at the local lunatic asylum, as you don't understand how to make a process easier. We will be reviewing on screen. The reason for this is that an audit trail can contain much more information that fits on a screen, and printing can generate much, much more paper than anticipated. When it comes to on-screen review, it is important that the reviewer has one and preferably two large high-resolution screens. Perhaps it is time to ask your boss for a 55 inch 8K TV, I mean monitor, for the review?

Seriously though, this is an important task and the reviewer needs the right tools. Having an expanded chromatogram on one screen and the pertinent audit trail events on another can help understand and recreate activities more easily than on one small monitor and save switching between views of the data. Comparison and correlation are much easier on two screens, and faster.

Next, let us look at where in the CDS application that there could be GMP-relevant modifications (remember, deletions are not configured for the users). Here are some changes that should trigger audit trail entries:

- Data entered manually and then corrected. Typographical errors will inevitably occur when data are entered manually into the sequence file. Ideally, they should be found by the performer of the test or the reviewer for the performer to correct. There will be corresponding audit trail entries with reasons for change.
- Failures of SST injections to meet acceptance criteria. There should be entries in the audit trail, but they also need to be cross referenced with entries in the instrument log together with any corrective action and any requalification work, such as replacement of pump seals.
- Changes to instrument and processing parameters, if allowed by the CDS
- Manual integration of peaks (if allowed) which will be the subject of a later Data Integrity Focus article.
- Changes to calculation formulae

These are some of the areas where there might be audit trail entries containing GMP-relevant changes.

"Typographical errors will inevitably occur when data are entered manually into the sequence file."

Review by Exception

Review by exception is a term used to review only the exceptions in any analytical run, rather than each and every audit trail entry. In the discussion above Annex 11 required an audit trail for GMP-relevant changes and deletions (6). If no deletions are allowed in the CDS, then all you need to look for are the modifications or the exceptions to normal working of the system.

Consider an analysis: if all peaks are integrated automatically, do you need to look at the audit trail entries for manual integration? No. Each peak integration shows if a baseline has been placed automatically or manually with the integration codes BB or Bb for example. In the former, both the start and end baselines have been determined by the system; in the latter case, the trailing baseline has been positioned by a chromatographer. This is a slow process of looking at each chromatogram individually, and is only marginally more interesting than watching paint dry.

Does the CDS Aid Review by Exception?

A much better approach is if the CDS can highlight that there is no manual integration at the injection level AND this function has been validated, if there are no exceptions (manual integration) for the run, and you don't need to review the pertinent audit trail entries.

The exceptions the reviewers should be identifying are the GMP relevant changes such as those listed in **Table II**. This is where the supplier of your CDS can be a great help or a hinderance to the second person review process. The technical controls built into the application are enabled and validated to highlight changes to data so that a reviewer can focus their attention on the key items. This is risk assessment in practice. The ways that an application can identify changes to data are color coding (for example, a traffic light approach with green indicating no changes, yellow to highlight any data modifications, and red for deletions), or by flagging data changes. This functionality is important to avoid the reviewer from drowning in data.

One area that will NOT be subject to review by exception and MUST be performed in all the second person reviews, even if there is no indication manual integration, is viewing all chromatograms on screen. This can be either singly or overlaid to ensure peak shape and resolution are as expected and consistent throughout the run. This is good analytical science, and must be performed for all analyses to ensure the integrity and quality of the results. There are no exceptions!

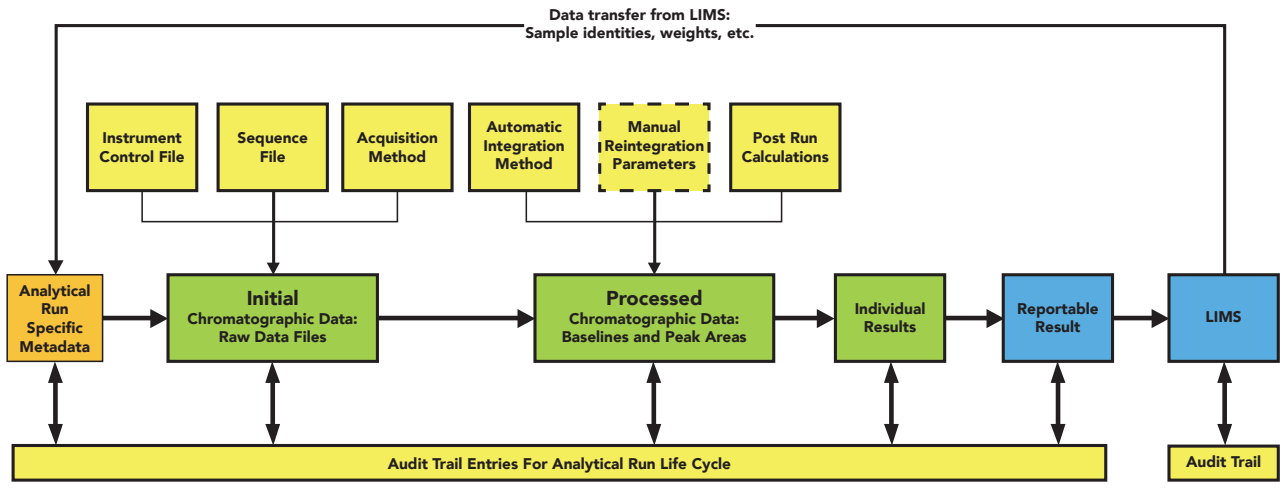
Documenting the Review

Few laboratory informatics applications have the ability to document if an audit trail has been reviewed, by whom, and when. Ideally, this is the best approach. However, in many cases, the review must be done procedurally, and the SOP must state that the meaning of the signature of the reviewer includes review of applicable audit trail entries. Sometimes, auditors insist that laboratories print out audit trail entries and sign them to provide documented evidence of the review. This approach should be resisted, as it is unrealistic and untenable, and laboratories should ask where is the specific regulation for this approach. This is an area where users require an electronic audit trail review function. In the absence of this, data integrity audits should focus on the effectiveness of a procedural audit trail review, and be conducted more frequently.

AT Review: System vs. Process

Up to now, we have just considered audit trail review in a CDS that is not interfaced to any other application. However, there are situations where a

Figure 2: Audit trail review when a LIMS is interfaced to a CDS.



CDS is interfaced to another informatics application, such as a laboratory information management system (LIMS); how should an audit trail review be conducted in this situation? We must consider process taking precedence over system when considering audit trail review.

Figure 2 depicts a LIMS interfaced with a networked CDS. As I mentioned above, we have to consider process, not system, otherwise potential issues will fall into the interfaces and not be identified in any review.

- The process starts in the LIMS, where sample weights and sample identities are downloaded to the CDS
- Any run specific metadata (such as, for example, dilutions) are manually entered into the sequence file of the CDS by the analyst
- The analysis takes place in the CDS, with the performer calculating the reportable result
- At the end of the analysis, the result is transferred automatically from the CDS to the LIMS.

Now, we have to consider how we need to conduct the audit trail reviews with the two systems. We will only focus on the transfers between the two at this point.

- The export of the sample identities and weights will be recorded in the LIMS audit trail, and there should be a corresponding import in the CDS audit trail
- Time (and date) synchronization is very important here. There should be a delay between the LIMS data

export and the import into the CDS; how much would be determinized in the validation of the interface (from microseconds to minutes, depending on the transfer mechanism). An important issue could be if the two systems were in different timezones; however, this should be already resolved in the system validation.

- At the completion of the analysis, there must be an export of the data from the CDS recorded in the CDFS audit trail, and, after a delay, an import into the LIMS, with a corresponding record in the audit trail.

Compliance Features to Consider When Purchasing a CDS

Apart from the chromatographic and instrument control functionality, one of the key requirements when selecting a new CDS are the technical control available to help protect electronic records, implement electronic signatures, and audit trail functionality. Ensuring regulatory compliance and data integrity are essential criteria for system selection now. These functions are often overlooked in selection of a CDS. Here are some of my compliance criteria that you should include when selecting a new system:

- Database as the foundation for managing data and building an effective audit trail.
- Flexible data storage to separate active data projects from inactive or archived ones.
- Configuration at the application level to protect electronic records.
- Configurable user roles or types to avoid conflicts of interest, such as, for example, no user should have administration privileges. Note that there will also be laboratory administrators for building custom calculations and reports.
- Audit trail functionality covering the whole system. Within this umbrella, there are two options: either a single audit trail for the application coupled with effective search routines to find all entries associated with a specific analysis; or two separate audit trails, one at the system level and one at the data level. When a project is created, it will have a data level audit trail within it, making it easier to search events within the analysis.
- Technical controls within the audit trail to highlight data changes and deletions to facilitate the review process, as well as enable review by exception, plus the ability to create efficient search routines within an individual project or the whole database to identify data trends and inconsistencies.

- Functionality within the CDS application to document that audit trail entries have been reviewed.

Summary

We have looked at the regulations and regulatory guidance for audit trail review, which is a key component for second person review of chromatographic analysis. To facilitate an effective review by exception, technical controls need to be included in the CDS application to identify data changed during an analytical run, including a function to document the review itself.

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

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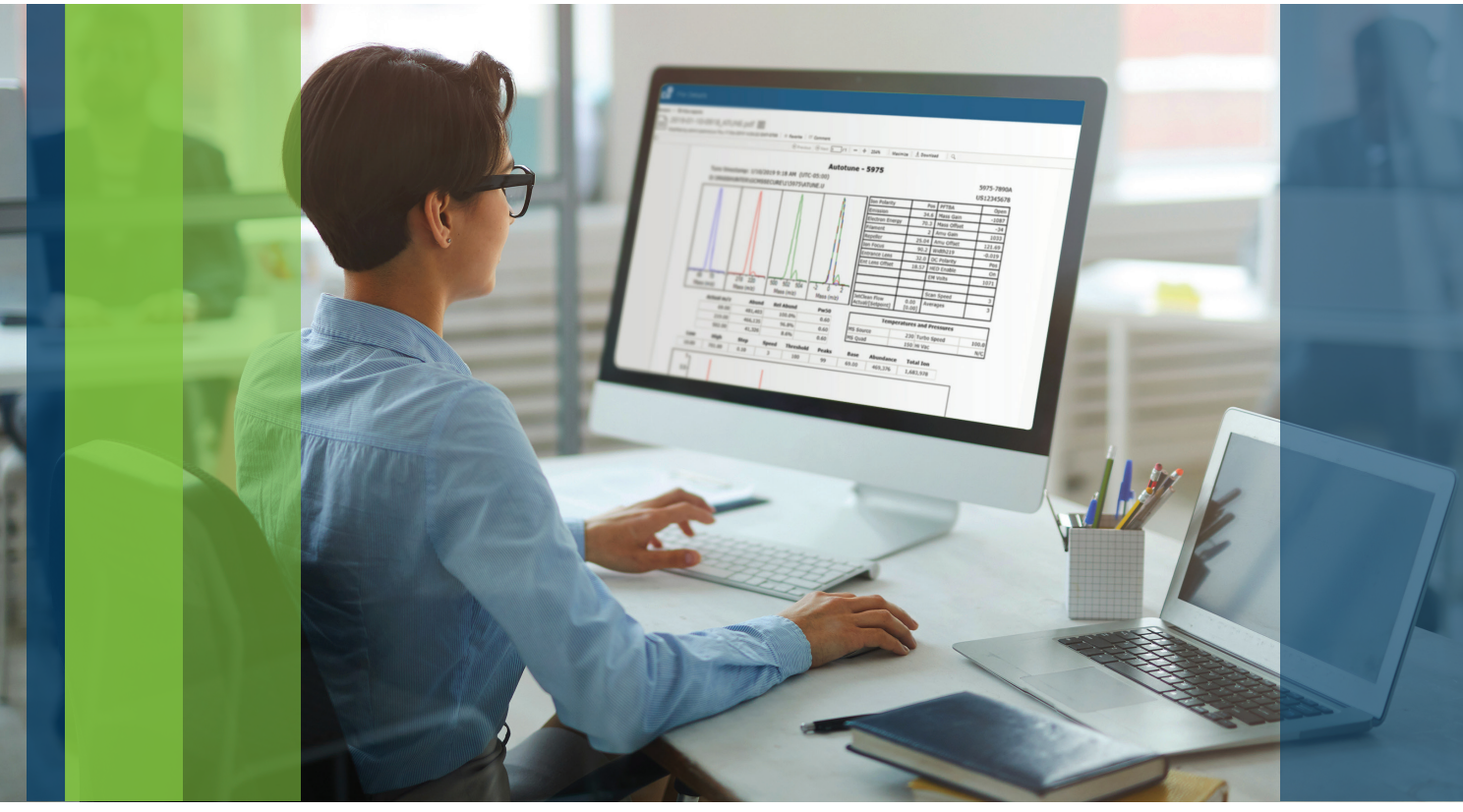

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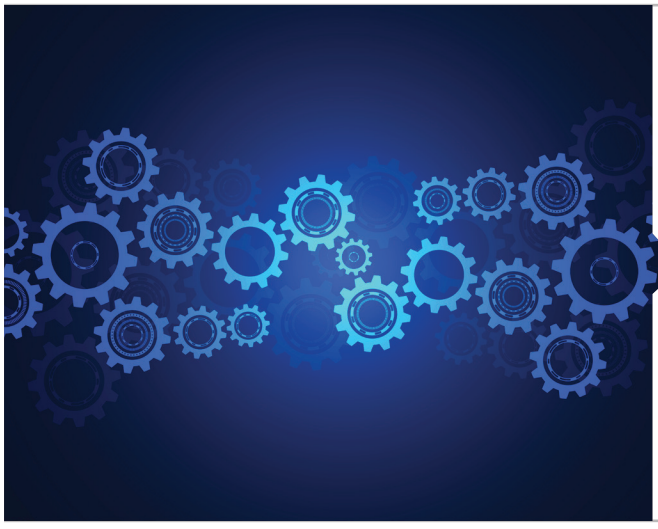

Understanding the Lifecycle Approach for Analytical Procedures

R.D. McDowall

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Accurate analytical analysis requires robust and validated analytical procedures. Change is underway in the approach to developing, validating, and using analytical procedures. Are you ready for the changes coming your way?

All analytical procedures should be fit for their intended use with appropriate measurement uncertainty (precision and accuracy), selectivity, and sensitivity. In this installment of "Data Integrity Focus," we look at the impact of an analytical procedure on the integrity of data produced in regulated good manufacturing practices (GMP) and good laboratory practices (GLP) laboratories. Within the framework of the Data Integrity Model (1, 2), there is the right analytical procedure for the job at Level 2. The use of an accurate procedure is built on the foundation layer of data governance with management leadership, quality culture, procedures for data integrity, and training. This is applied to getting the right analytical instrument and application software that are qualified and validated respectively. Both levels now need to be applied to the development, validation, and use of any analytical procedure.

Analytical Procedure or Method?

You will notice that the title of this article uses the term analytical procedure, and not analytical method. The reason is that an analytical procedure covers all stages from sampling, transport, storage, preparation, analysis, interpretation of data, calculation of the reportable result, and reporting. An analytical method is a subset of this, and is typically interpreted as the instrumental analysis phase. After a discussion of the applicable regulations

and guidance, I will focus on the analytical method portion of a procedure. After all, this is LCGC!

GMP Regulatory Requirements for Analytical Procedures

In 21 *CFR* 211.194(a), there is the following requirement for analytical methods used in pharmaceutical analysis:

> *(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: …..*
>
> *(b) A statement of each method used in the testing of the sample.*
>
> *The statement shall indicate the location of data that establish that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested…..*
>
> *The suitability of all testing methods used shall be verified under actual conditions of use (3).*

What does this mean in practice? Any laboratory must know where the validation was carried out so that an inspector can access the data plus any method transfer protocol that was performed with the associated report to show that the procedure works in a specific laboratory. This interpretation is mirrored in EU GMP Chapter 6 on Quality Control, where clause 6.15 states:

> *Testing methods should be validated.*
>
> *A laboratory that is using a testing method and which did not perform the original validation, should verify the appropriateness of the testing method.*
>
> *All testing operations described in the marketing authorization or technical dossier should be carried out according to the approved methods (4).*

Reinforcing the European requirement, there is also EU GMP Annex 15 on Qualification and Validation, a very generic set of requirements covering all possible processes and equipment, where Section 9.1 notes for test methods:

> *All analytical test methods used in qualification, validation or cleaning exercises should be validated with an appropriate detection and quantification limit, where necessary, as defined in Chapter 6 of the EudraLex, Volume 4, Part I (5).*

However, these regulations give broad direction, but not much detail. What do we need to do to validate an analytical procedure or test method?

GMP Regulatory Guidance for Validation

Currently in GMP, there is ICH Q2(R1) for method validation (6) that outlines the requirements for method validation for quality control (QC) testing. The emphasis in the document is mainly on chromatographic methods of analysis with parameters such as repeatability, intermediate precision, limits of quantification (LOQ), and limits of detection (LOD). There is no mention of method development in the guidance. However, there is an almost ritualistic approach to interpreting ICH Q2(R1): "If it says it, do it."

Therefore, we can find the stupid situation when validating a method for an assay of active component between say 90 and 110% of label claim, that the method also includes determination of LOQ and LOD. Why determine such parameters when the method will never be used near them? It is in ICH Q2(R1)" is always the answer. This is mirrored in EU GMP Annex 15, where at first reading all analytical procedures appear to require LOQ and LOD determination. However, the requirement does say "as appropriate." Does anyone ever engage the brain and think in these situations?

In 2000, the FDA issued a draft guidance for industry on Analytical Procedures and Methods Validation (7) that outlined the FDA expectations for validation. The main problem is that this guidance did not address one of the most critical stages of the whole process: method development. In 2015, the FDA replaced the 2000 draft guidance with yet another draft guidance entitled "Analytical Procedures and Method Validation for Drugs and Biologics" (8), where there is a little, but insufficient, section on method development.

Bioanalytical Method Validation Guidances

In the bioanalysis field, there are guidances issued by the EMA and FDA. The European Medicines Agency Guideline on Bioanalytical Methods Validation from 2011 states in Section 4.1 (9):

> *A full method validation should be performed for any analytical method whether new or based upon literature.*
>
> *The main objective of method validation is to demonstrate the reliability of a particular method for the determination of an analyte concentration in a specific biological matrix, such as blood, serum, plasma, urine, or saliva. Moreover, if an anticoagulant is used, validation should be performed using the same anticoagulant as for the study samples. Generally, a full validation should be performed for each species and matrix concerned.*

"All the emphasis is on the validation, rather than the development of the assay."

The final version of the FDA Bioanalytical Methods Validation guidance for industry in 2018 contains in the section on Guiding Principles the following selected statements (10):

> *The purpose of bioanalytical method development is to define the design, operating conditions, limitations, and suitability of the method for its intended purpose and to ensure that the method is optimized for validation.*
>
> *Before the development of a bioanalytical method, the sponsor should understand the analyte of interest (determine the physicochemical properties of the drug, in vitro and in vivo metabolism, and protein binding) and consider aspects of any prior analytical methods that may be applicable.*
>
> *Method development involves optimizing the procedures and conditions involved with extracting and detecting the analyte. Bioanalytical method development does not require extensive record keeping or notation…..*

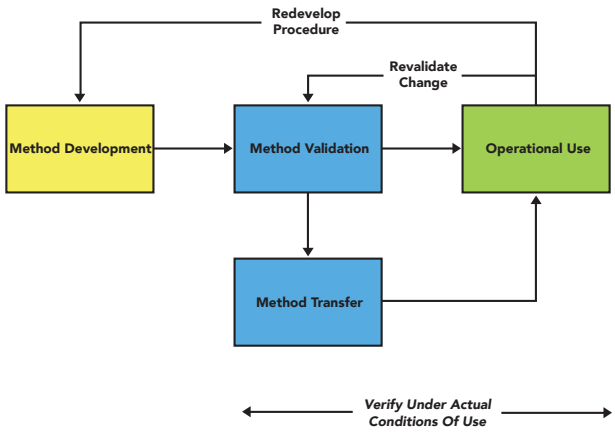
While this FDA guidance has started to include method development, it notes that documentation of this work does not need to be extensive. As we shall see later, this is the wrong approach to take, as method development is the single most important phase of an analytical procedure life cycle. Get this right, and the validation and operation of the method are easier to handle than a rushed development and validation. If a rushed approach is taken, then the analysts using the method pick up the tab with variable results and out-of-specification investigations.

In 2019, ICH M10 on Bioanalytical Method Validation reached step 2b and was issued for public consultation. Out of 60 pages, method development receives a scant half a page mention along the lines of FDA and EMA above and noting that:

> *Bioanalytical method development does not require extensive record keeping or notation (11).*

All the emphasis is on the validation, rather then the development of the assay. As we shall see, this is not the smartest approach, especially the majority of bioanalytical methods can be measuring analytes in biological matrices at the LOQ of the method. You really need to know what factors you need to control in the method, rather than hoping for the best.

Figure 1: A traditional view of analytical method development, validation, and use.



Traditional View of Development, Validation, and Use

Continuing this theme, the traditional view of analytical method development, validation, and use is shown in **Figure 1**. The main emphasis is on a rapid method development phase and validation by an analytical development group. This is followed by a formal transfer to a quality control group to demonstrate that the method (possibly) works in their laboratory and then operational use by the QC staff. If changes are required, these need to be validated, and a method may need to be redeveloped in light of experience with use. As we shall discuss at the end of this article, most methods are regulated for the pharmaceutical laboratory, and need regulatory approval for any major change. How can this be simplified?

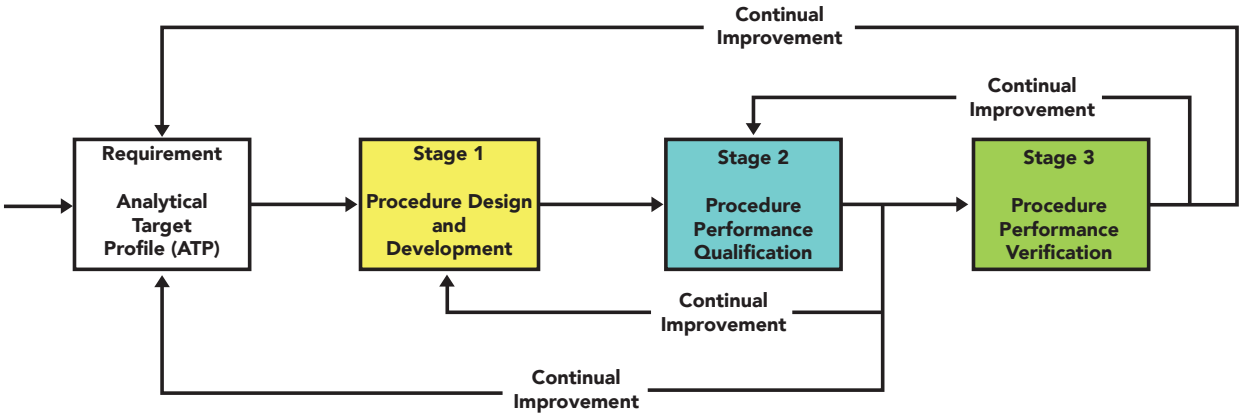
USP is Changing to a Lifecycle Approach

For 10 years, USP expert panels and committees have been publishing stimuli articles on analytical procedure lifecycle management (APLM). This new approach comes from the FDA's updated guidance on process validation that took a lifecycle approach to the topic, rather than "three validation batches and all is good." In addition to the "Stimuli to the Revision Process" articles published in *Pharmacopoeial Forum*, there is also a draft *USP* <1220> on Analytical Procedure Lifecycle Management issued for public comment in 2017 (12). At the end of this year, a revised draft of *USP* <1220> is expected to be published for comment.

The principles outlined in the current draft *USP* <1220> are a Quality by Design (QbD) approach to method development and validation (12) that is intended to deliver more robust analytical procedures. There is greater emphasis on the earlier phases of the lifecycle of an analytical procedure, such as defining the procedure specification in an Analytical Target Profile or ATP.

"Most methods are regulated for the pharmaceutical laboratory, and need regulatory approval for any major change."

Figure 2: Proposed *USP* <1220> process for analytical procedure lifecycle management.



The overall process is shown in **Figure 2**. Although the USP is focused primarily on compendial analytical procedures, the sound scientific principles outlined in the draft USP <1220> are, in my view, applicable to bioanalytical methods as well. Shown also in the figure are the feedback loops from stage 3 to stage 2 and from stage 2 to stage 1, as well as to the ATP, representing continual improvement of the procedure. The key is continual improvement, as the pharmaceutical industry is regulated and some procedures that are part of a registration dossier might need to be modified under change control.

Stages of the Analytical Procedure Lifecycle

The lifecycle of analytical procedure advocated by *USP* <1220> in **Figure 2** consists of three stages:

1. Procedure Design and Development (method development) derived from the ATP
2. Procedure Performance Qualification (method validation)
3. Procedure Performance Verification (Ongoing assessment of the procedure performance).

We are not very good at method development or monitoring performance of an analytical procedure in use. This new approach aims to provide a sound scientific basis throughout the whole analytical procedure lifecycle. We will discuss each stage of the lifecycle in overview; for a more detailed understanding of the *USP* <1220> process and best practices in analytical

procedure validation, the reader is referred to the book by Ermer and Nethercote (13).

Define the Analytical Target Profile

First, we need to define what are the objectives of the procedure and this is achieved by writing an Analytical Target Profile (ATP), as shown in **Figure 2**. An ATP should be considered the specification or intended use for any procedure. This term was developed by a US and EU pharmaceutical industry working group on Analytical Design Space and Quality by Design of Analytical Procedures, and has been incorporated by the USP into two Stimuli to the Revision Process articles on the ATP, as well as the draft USP general chapter <1220> (12–15).

The Analytical Target Profile (ATP) for an analytical procedure is a predefined objective of a method that encapsulates the overall quality attributes required of the method, including:

- sample to be tested
- matrix that the analyte will be measured in
- analyte(s) to be measured
- range over which the analyte(s) are to be measured for the reportable result
- quality attributes such as selectivity and precision and accuracy of the whole procedure or total measurement uncertainty (TMU).

This is the core of the lifecycle approach, as it defines the high-level objectives with no mention of any analytical technique used to meet the ATP as this could bias the analytical approach.

An example ATP could be:

> *To quantify analyte X over a range between a% and b% (or whatever units are appropriate) with X% RSD precision and Y% bias in a matrix of Z (or in the presence of Z).*

This means that the requirements for an analytical procedure are defined before any practical work begins, or even an appropriate analytical technique has been selected. It provides the method developer with an explicit statement of what the procedure should achieve. This is a documented definition, and can be referred to during development of the procedure or revised as knowledge is gained.

Stage 1: Procedure Design and Development

This is most important part of an analytical procedure lifecycle, but it is missing from or minimal in the current regulatory guidance documents described above. Knowing how sampling, transport, storage, instrumental analysis parameters, and interpretation of data impact the

reportable value is vitally important to reducing analysis variability, and hence out-of-specification (OOS) results. The aim of a Quality by Design (QbD) approach is a well understood, controlled, and characterized analytical procedure, and this begins with the design and development of the procedure.

Knowledge Gathering

From the ATP we need to gather information and knowledge to begin the initial procedure design, such as:

- chemical information about the analytes of interest, such as structure, solubility, and stability (if known)
- literature search (if a known analyte) or discussions with medicinal chemists (if a new molecular entity, or NME).

From this knowledge, coupled with the ATP, the most appropriate procedure including the measurement technology can be derived, such as:

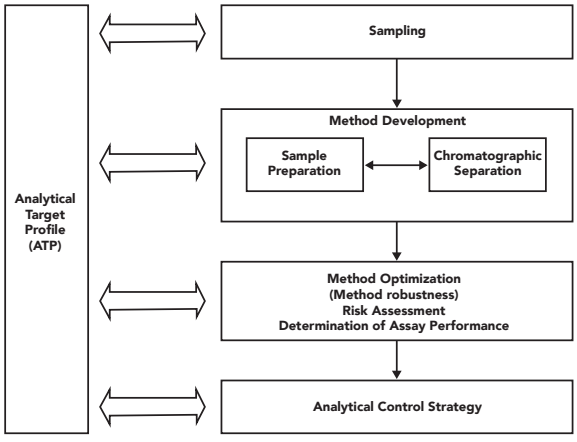
- type of procedure (for example, assay or impurity) in an active pharmaceutical product or determination of an NME in animal or human plasma.
- sampling strategy, such as the sample amount or volume required, how the sample will be taken, any precautions required to stabilize the analyte in the sample, and other factors
- design of the sample preparation process to present the sample to the instrument
- whether there is any need to derivatize the analyte to enhance detection characteristics
- appropriate analytical technique to use based upon the ATP and the chemical structure of the analyte (including, but not limited to, LC-MS, LC-UV, and GC-FID)
- an outline of separation needs based on previous analytical methods with analytes of similar chemical structure, if appropriate.

In addition, business factors such as time for the analysis and cost should be considered when developing a method. Quicker is better, provided that the ATP is met, and UHPLC may be a better alternative to conventional HPLC, as an example.

Initial Design of the Analytical Procedure

Assuming that we are dealing with a liquid chromatographic analysis, solid samples need to be prepared so that a liquid extract can be introduced into the chromatograph for analysis. Development of the sampling, sample preparation, and separation should proceed in tandem and iteratively as shown in **Figure 3**. Some

Figure 3: Method development workflow for an HPLC procedure (13).



considerations for this phase of the development, covering all sample types and concentration or amount ranges defined in the ATP are:

- How much sample is required to achieve the ATP?
- Does the sample have to be dissolved, homogenized, sonicated, or crushed before sample preparation can begin?
- Does the analyte require derivatization either to stabilize the compound, or to enhance limits of detection or quantification?
- Screening experiments are run to see how the analytes run on a variety of columns and mobile phases of varying composition of organic modified and pH value of the aqueous buffers. It is important to note here that the KISS (Keep It Simple, Stupid) principle applies here. Don't overcomplicate a method, as it will usually need to be established in one or more other laboratories, and unnecessary complexity makes method transfer more difficult.

A better approach for method screening is to automate it, using method development software to design and execute experiments using a statistical design (for example, factorial design such as Plackett-Burman). This is a more expensive option, but it will produce design space maps for optimum separation much faster than a manual approach. These design space maps provide the basis for a robust separation as the factors controlling the separation can be more easily identified and the optimum separation to meet the ATP can be predicted and then confirmed by experiment.

The overarching principle in method development and optimization is to keep the method as simple as possible to achieve the ATP requirements. For example, a commonly available column and simple mobile phase preparation should be the starting point for most separations, depending, of course, on the type of analyte involved. Use isocratic elution to achieve the ATP rather than a gradient, as the latter will increase the overall analysis time.

Table I: C, N, X classification of method variables

Method Variable	Classification
Controlled (C)	• Explicit instructions in the analytical procedure • Setting the value of an instrument param-eter, for example, detector wavelength
Noise (N)	Variable difficult to control or predict and may vary randomly: • Common variations are investigated experimentally, for example, precision
Experimental (X)	Variable that can varied deliberately • Impact is investigated by experiment, for example, stability and robustness • Establish acceptable ranges of performance

Risk Assessment and Management

Management of risk is a key element in the analytical procedure lifecycle approach. This involves identifying and then controlling factors that can have a significant impact on the performance of the separation. Such factors may be:

- pH value of the aqueous buffer or proportion of organic modifier used in an LC mobile phase
- type or dimensions of the column used
- autosampler and column temperature
- impact of light during sampling or sample preparation.

A formal risk assessment can be undertaken, such as Failure Mode Effects Analysis (FMEA), to identify the risk with the highest impact (13). The aim of risk assessment is to either mitigate or eliminate the risk posed by variables in the sample preparation, instrumental analysis, or operating practices. Method variables can be classified as controlled, noise, or experimental (C, N, or X), as shown in **Table I**. A discussion of how these variables are investigated is outside the scope of this article, and the reader is referred to Ermer and Nethercote's book for more details (13).

When key variables have been identified, then robustness studies can be started to understand the impact of each one on the overall analytical procedure. There will be a study design for robustness experiments, and the results will be examined statistically. The aim is to identify the acceptable range of each key variable; the greater the range means that the method is more flexible. Again, please see Ermer and Nethercote for more information about this approach (13).

Analytical Control Strategy: Identifying and Controlling Risk Parameters

The analytical control strategy for each procedure is based on the outcome of the risk assessment and, where appropriate, in combination with the robustness studies. This should provide a list of method parameters and variables that have significant impact on the method, and its performance as well as what to avoid when executing the analytical procedure. The outcome is the establishment of controls for critical parameters, such as how to perform a specific task with sufficient detail to ensure consistent performance, the type of integration, conditions in the procedure that have significant effects, or steps to avoid certain situations where outside variables (light, for example) can affect the stability of the analyte.

The outcome of the analytical control strategy is to have a set of instructions that are explicit and unambiguous when executing the procedure, such as:

- how to sample and the required sample size
- specification of sample containers, transport conditions to the laboratory, and storage conditions
- preparation of the sample for analysis
- preparation of reference standard solutions and mobile phases
- performance of the analysis, as well as integration and interpretation of data
- calibration method used
- identification of the system suitability test (SST) parameters to be used, and determination of the acceptance criteria for each one.

Procedure Development Report

The outcome of Stage 1 should be a comprehensive method development report describing the optimized procedure. It should also contain practical details for the procedure, including the robustness of the analytical procedure, the analytical control strategy and the SST parameters to be used, and their acceptance criteria.

This is in stark contrast with the FDA bioanalytical method and draft ICH M10 guidance documents that suggest that bioanalytical method development does not require extensive recordkeeping or notation (10,11). If you don't have any understanding of how critical parameters impact the performance of an analytical procedure, then how can you control them? In my opinion, method development needs a report that highlights those key parameters, and how they impact performance of the procedure. It is good analytical science, and an essential reference for all further work.

Stage 2: Procedure Performance Qualification

Planning the Validation

Procedure Performance Qualification (PPQ) or method validation should be simply confirmation of good method development and demonstrate that the analytical procedure is fit for purpose. PPQ demonstrates that the developed analytical procedure meets the ATP quality attributes, and that the performance is appropriate for the intended use. To control the work, there will be a validation plan or protocol describing the experiments to be performed, with predefined acceptance criteria to demonstrate that the ATP has been met. This will depend on the type of procedure, such as active pharmaceutical ingredient (API), impurities, or bioanalysis. The various experiments will depend on the criteria described in the ATP, and on the intended use of the procedure. For example:

- Linearity experiments should be used to support the use of the specific calibration model used in the procedure (the calculations for which have been verified in Level 1 in the computerized system validation of the data system used for this work).
- Specificity or selectivity (depending on whether the instrumental technique is absolute or comparative) must be determined, including resolution for impurities and peak purity assessment for stability-indicating methods.
- Precision (injection precision, repeatability, and intermediate precision) should be set. The minimum number of runs could be two, but four or more provides better understanding of the intermediate precision for routine use
- Accuracy can be run in the same experiments as precision.
- Analyte stability under storage, laboratory, and instrument conditions must be determined.
- System suitability test parameters, and their acceptance criteria, will be verified during this work

It is important that the acceptance criteria be defined in the validation plan, and are based on the information gathered

"To control the work, there will be a validation plan or protocol describing the experiments to be performed, with predefined acecptance criteria to demonstrate that the ATP has been met."

from Stage 1, the procedure design and development. The plan will also define how the data from the various experiments will be evaluated statistically against the acceptance criteria.

Validation Report

Once the work is completed, a report is written that describes the outcome of the validation experiments and how the procedure meets the requirements of the ATP.. As the draft *USP* <1220> (12) notes:

> *The analytical control strategy may be refined and updated as a consequence of any learning from the qualification study. For example, further controls may be added to reduce sources of variability that are identified in the routine operating environment in an analytical laboratory, or replication levels (multiple preparations, multiple injections, etc.) may be modified based on the uncertainty in the reportable value.*

The scope and the various parameters with the acceptance criteria for a bioanalytical method validation report are defined extensively in the updated FDA Guidance for Industry on Bioanalytical Method Validation and the draft ICH M10 guidance documents (10,11).

Analytical Procedure Transfer

Analytical method transfer is not always easy or straightforward, because there are always items that are not well described in, or even omitted altogether from, an analytical procedure. Well-documented method development (if existing) and validation reports will aid the transfer process immeasurably. The transfer must be planned, and a protocol developed, between the originating and receiving laboratories that includes predefined ways that the data will be interpreted with acceptance criteria. A report should be produced summarizing the transfer results against the data generated by the receiving laboratory.

To reduce the effort required when transferring an analytical procedure to another laboratory, a subject-matter expert could travel to the receiving laboratory to provide help and advice. Alternatively, an analyst from the receiving laboratory could go to the originating laboratory to learn the procedure. Management often looks at the up-front cost of this, but dismisses the hidden cost of time wasted in transferring the method without help from the originating laboratory.

When considering method transfer, one of the issues when using a contract research organization (CRO) laboratory is the quality of the written procedure used for method transfer. Often the originating laboratory

(sponsor) may make a minimal effort at validation before passing the procedure to a CRO to complete the development and validation. This is not the best approach, and is planning for failure.

Stage 3: Procedure Performance Verification

Routine monitoring of an analytical procedure's ongoing performance is an important element in maintaining control over the analytical procedure in operational use. It provides assurance that the analytical procedure remains in a state of control throughout its lifecycle, and provides a proactive assessment of a procedure's performance. The aim of verification is that the reportable result is fit for purpose and can be used to make a decision.

Part of this verification can be trending of SST and sample replicates results over time. However, there is a note of caution that SST results can also be used to measure instrument performance directly (Group B and some Group C instruments) or indirectly (some Group C instruments) as part of an ongoing performance qualification. Data that could be collected and tracked are:

SST test results including failures

Trending of individual results and the reportable result including OOS and outputs from investigations.

These data should be monitored against limits, so that when there is a trend indicating a parameter is out of control, an investigation can be started early, before the situation gets out of hand (a proactive, rather than reactive, approach). When a root cause is identified in an investigation, it may be appropriate to update the analytical control strategy or to update the analytical procedure.

Pharma Is Going Lifecycle

Why have I discussed this new approach? The pharmaceutical industry is going lifecycle! ICH published in November 2019 a new guidance, ICH Q12, entitled "Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management" (16). This document provides a framework to facilitate the management of post-approval Chemistry Manufacturing Controls (CMC) changes in a more predictable and efficient manner and the key concept is Established Conditions (ECs) for analytical procedures:

> *ECs related to analytical procedures should include elements which assure performance of the procedure. The extent of ECs and their reporting categories could vary based on the degree of the understanding of the relationship between method parameters and method performance, the method complexity, and control strategy (16)*

Note that ECs are legally binding, as they will be part of a drug license application and changes will need regulatory approval. ECs are built up during the development and validation process of the lifecycle.

In addition, to further support the analytical procedure lifecycle management (APLM) approach, ICH is undertaking two projects:

- An update and expansion of ICH Q2(R1) to include other analytical techniques with a possible release for public comment of Q2(R2) as early as the end of this year (17)
- ICH Q14 on Analytical Procedure Development, which is beginning to be developed (18).

Common sense would suggest that combining the two into a single document would be the best approach. However, putting common sense and regulatory compliance in the same breath would be a novel idea.

What this means in practice is that the more you know about your analytical procedure, the more predictable the analysis becomes, thanks to the lower variation. There should be a lower regulatory burden to change a registered method. Most importantly, with robust analytical procedures there should be a lower incidence of OOS results attributed to analytical variation and subsequent investigations. OOS will be the subject of an article later in our series.

Summary

A key component for data integrity is accurate and precise analytical procedures that are validated for intended use. Changes in the way procedures are specified, developed, validated, and operated are coming. This "Data Integrity Focus" article should help prepare you for the changes.

Acknowledgments

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

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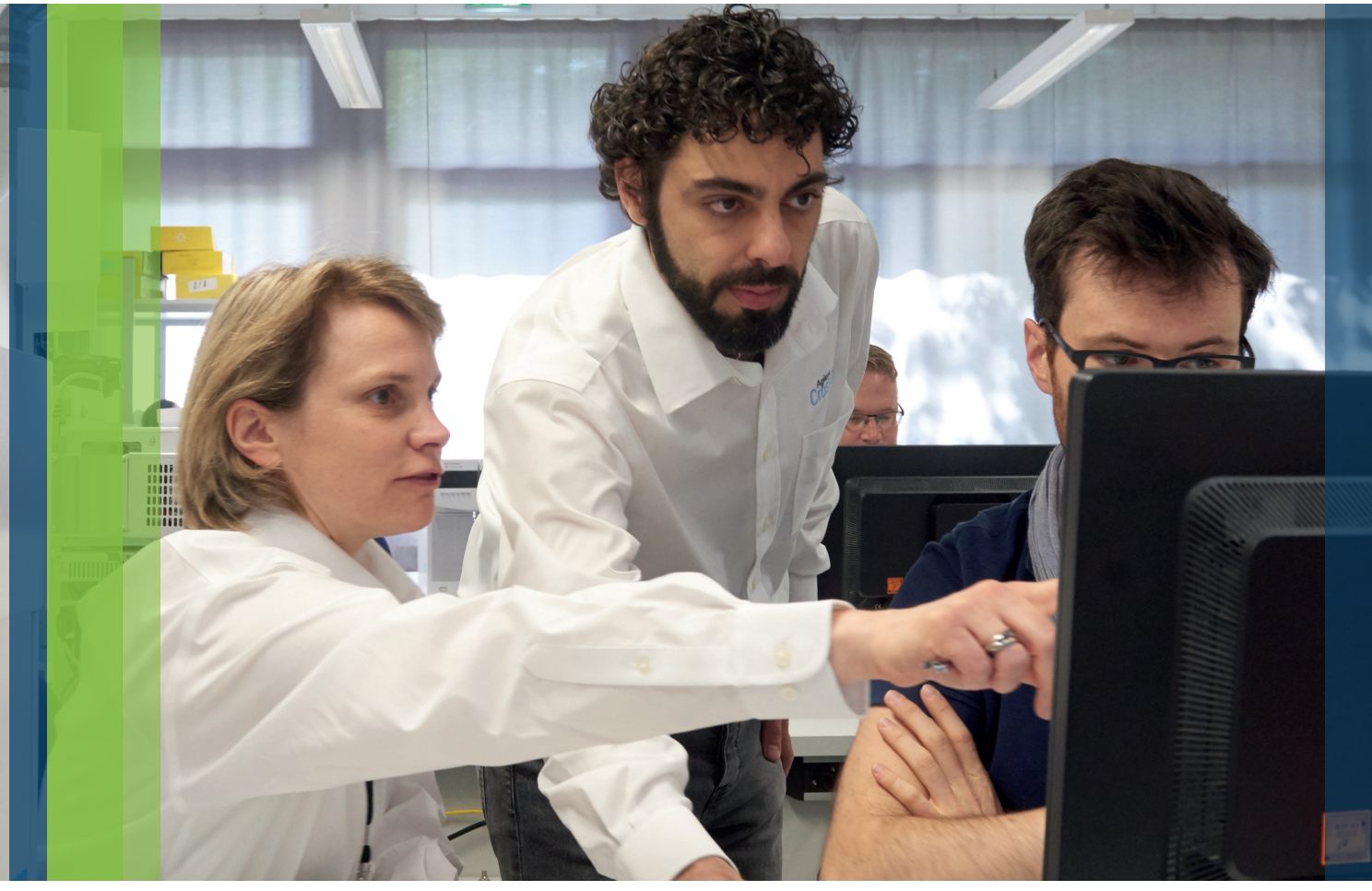

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