

# The Role of Analytical Instrument Qualification in Data Integrity With the 2017 Version of USP <1058>

## Authors

Dr. R. D. McDowall  
R. D. McDowall Limited, UK  
P. A. Smith  
Agilent Technologies, Inc.

## Introduction

US Pharmacopeia (USP) general chapter <1058> on Analytical Instrument qualification (AIQ) was first implemented in 2008 and remained unchanged for nine years. During 2017, the USP implemented two updates to <1058>. These updates have a significant impact on AIQ, and as the only major pharmacopeia with a chapter dedicated to AIQ, changes to USP <1058> are of global significance.

To help regulated laboratories fully comply with 2017 <1058> requirements, Agilent has produced four White Papers with compliance consultant Bob McDowall, who has been closely involved with the development of <1058>. The series includes:

1. What Has Changed with the 2017 Version of USP <1058>?<sup>1</sup>
2. How to Comply with the 2017 Version of USP <1058>?<sup>2</sup>
3. The Role of Analytical Instrument Qualification in Data Integrity with the 2017 Version of USP <1058>?<sup>3</sup>
4. What Does Performance Qualification Really Mean with the 2017 Version of USP <1058>?<sup>4</sup>

In 2017, a new version of USP <1058> on Analytical Instrument qualification (AIQ) became effective<sup>5</sup>. The changes in the general chapter are discussed in the first White Paper of this series: *What has Changed with the New Version of USP <1058>?*<sup>1</sup>. This White Paper considers the relationship between AIQ and data integrity, and discusses what a laboratory must do to ensure that qualified analytical instruments and validated computerized systems are set up and configured to help ensure data integrity.

## Data integrity: the audit focus area in the pharmaceutical industry

Since the Able Laboratories fraud case of 2005<sup>6</sup>, data integrity has become the central focus for audits of regulated laboratories. Inspectorates around the world have been trained in data integrity auditing, with a focus on electronic records rather than paper printouts. Figure 1 shows the trend line for the number of FDA data integrity related warning letters issued each year from 2005 to 2017.

Similar data integrity trends are observed in other regulatory data, such as EudraGMDP noncompliance reports, providing unambiguous evidence of increasing numbers of reported data integrity violations. In response to this trend, the volume of data integrity guidance documentation issued by MHRA<sup>7</sup>, FDA<sup>8</sup>, WHO<sup>9</sup>, PIC/S<sup>10</sup>, EMA<sup>11</sup>, and GAMP<sup>12</sup> has grown.

## Laboratory compliance: example audit findings

The continued focus on analytical laboratories during audits and inspections is evident when the contents of regulatory noncompliance are examined in more detail. Table 1 in Appendix 1 contains a selection of recent laboratory compliance nonconformances. This information is from:

- FDA Warning Letters
- FDA 483 observations
- EudraGMDP noncompliance database

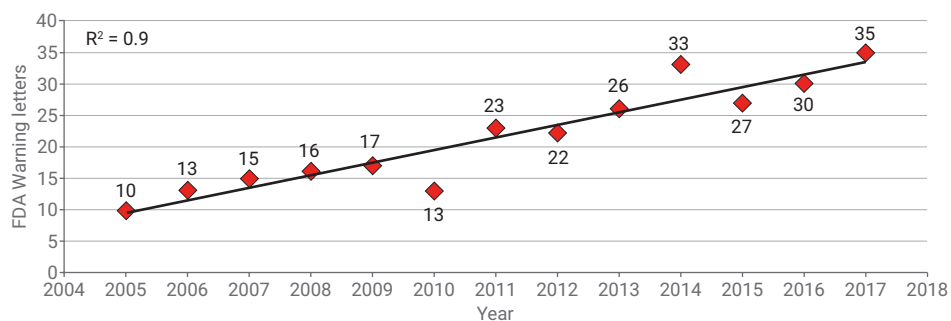


Figure 1. Trend in data integrity related FDA warning letters.

Many data integrity related FDA warning letters have focused on Chromatography Data System (CDS) use, and Table 1 contains some examples of this:

- **Accurate:** Example 19
- **Audit trail review:** Example 25
- **Calibration failure:** Examples 12, 15
- **Contemporaneous—date/time manipulation:** Examples 3 and 10
- **Data backup:** Example 14
- **File deletion:** Examples 2, 5, 13, 24
- **Manual integration:** Example 22
- **Shared passwords:** Example 16
- **System suitability:** Example 18
- **Trial injections:** Example 23
- **Invalidated software:** Examples 11, 27
- **Instrument qualification:**
  - **Data integrity:** Examples 4, 17
  - **Incomplete:** Example 1, 7
  - **Inconsistent:** Example 1
  - **Not done:** Examples 8, 9, 11
  - **No PQ:** Examples 6, 29, 30
  - **Range of use:** Examples 26, 28
  - **Suitability of equipment:** Example 20
  - **Use of unverified software functions:** Example 21

These nonconformances (see Table 1) provide evidence of the level of detail in which regulators are examining during audits. As an indication of current FDA thinking, the warning letter referenced in example 22 (from November 2017) in Table 1, cites the lack of “an approved protocol for manual integration or quality oversight of the practice”. This is specifically mentioned, even though the warning letter begins with significant nonconformances about process validation. Example 20 is significant because, in response to the warning letter observation about out of specification (OOS) practices, the company was asked to provide information that included suitability of the instrumentation. Auditors are focusing on laboratory operations in greater detail.

The 2017 update to USP <1058> is expected to bring AIQ into even greater focus during laboratory audits and inspections. Aligning AIQ practices with <1058> will become increasingly important.

When reviewing nonconformance data and violations, it is important to understand that the regulatory violation will be documented, but not the underlying root cause. Example 16 in Table 1 lists the use of shared login account information (so work is not attributable to an individual) as the

violation, but does not list the root cause. The root cause is unknown (outside of the organization receiving the citation), but could be because the laboratory is using software lacking appropriate (or poorly implemented) technical controls, or because the laboratory was trying to save money on user licenses. Such examples clearly demonstrate that the software had not been validated for intended use, or problems such as this would have been identified and corrected during the validation work. Data Integrity is driving a renewed interest in software validation (for instance, see Example 11 in Table 1).

The response a company provides to a nonconformance or quality deviation, should be addressed in the organization's Corrective Action, Preventive Action (CAPA) system. A good CAPA response to an audit investigation, such as an FDA 483, can limit escalation of the 483 into an FDA Warning Letter or other FDA action<sup>13</sup>.

Much of the laboratory software currently in use may not have been developed with data integrity compliance as the core focus. For example, some software may lack the functionality to electronically record audit trail reviews. For a discussion of the design of an ideal chromatography data system, see the four-part series by McDowall and Burgess<sup>14</sup>.



All laboratory processes, analytical instruments, and computerized systems need to be installed, configured, and validated to ensure the integrity of all data generated in a regulated laboratory. As inspections and audits are based on sampling a proportion of a company's systems in the time available, the risk is that any data integrity problems identified can cast a shadow of uncertainty over all the work of the laboratory:

*"...that raises concerns about the integrity of all data generated by your firm."* (FDA Warning Letter, Reference: ucm397054)

It is important to ensure that analytical instruments are qualified and configured to ensure data integrity during intended use, rather than using default software settings and configurations that were applied during initial installation.

## Data integrity: a model for understanding

The large volume of data integrity guidance listed in the reference section is subject to regular updates. This means that there are hundreds of pages of data integrity guidance, with more being added regularly. The problem for laboratories is how to interpret and understand such a large volume of nonharmonized information in a way that is of practical benefit to them.

Figure 2 shows the data quality triangle from USP <1058>, and demonstrates that AIQ is the foundation for quality laboratory data.

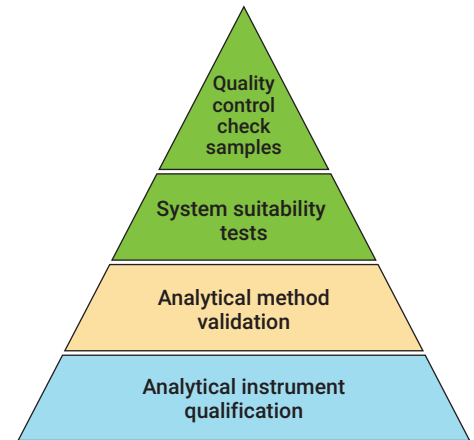


Figure 2. Data quality triangle from USP <1058>.

- The principles of the data quality triangle apply to all laboratories:
- AIQ is the base for quality analytical data
- Hierarchy of layers:
  - Instruments must be qualified
  - Method validation uses qualified instruments
  - Samples are tested using validated methods
  - System suitability and control samples demonstrate that the system is working when used
- All layers are required

Color has been applied to the levels in Figure 2 to demonstrate the relationship between the principles of the data quality triangle and the four-layer data integrity model shown in Figure 3.

This four-layer model is a way of taking all areas of the guidance documents and presenting them in a data integrity model under the company's pharmaceutical quality system. Each level supports the level above it and interacts with the layer above or below it. If the foundation is not right, the levels above are liable to collapse, despite the best efforts of the staff. Each layer of the data integrity model is explored with a focus on Level 1 to see how USP <1058> can help.

The data integrity model is analogous to building a house; if the lower level is faulty, the house collapses. The model starts at the foundation and builds up as follows:

- **Foundation—Right data governance:** The foundation is essentially data governance that impacts all functional groups within an organization. This is associated with creating the right culture for data integrity, and requires management leadership to create an open culture that allows people to admit mistakes and document the actions required. This is coupled with data integrity policies and procedures with effective training in data integrity and monitoring of adherence to them.
- **Level 1—Right instrument and system for the job:** Qualification and validation of analytical instruments and computerized systems, respectively
- **Level 2—Right analytical procedure for the job:** Here, the analytical procedures (for example, Methods) used for sample analysis are developed and validated or verified for operational use.
- **Level 3—Right analysis for the right reportable result:** Samples are taken to demonstrate adequate product quality and conformance with the product Marketing Authorization or Product License.

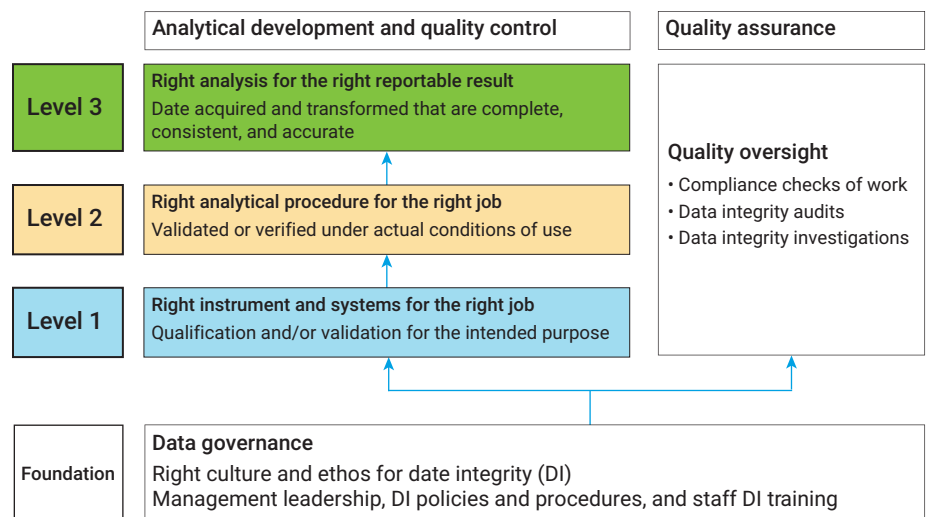


Figure 3. A data integrity model (adapted from CDS2 reproduced with permission RSC).

- **Quality assurance—Across the organization:** Shown on the right in Figure 3, the QA function is pervasive throughout the organization (Foundation layer and Levels 1–3) to provide quality oversight, for example, ensuring compliance with regulations, policies, and procedures as well as performing audits, periodic reviews, and data integrity investigations.

## What has changed?

The risk with most data integrity assessment and remediation programs is that business pressures can push companies to look for quick remediation at the lowest cost. This creates the potential for companies to explore how to fix the problem without necessarily identifying the underlying root cause. For example, upgrading or replacing noncompliant software for improved technical controls (for instance, 21 CFR Part 11 Compliance) can be an essential step to reduce data integrity risks, but in isolation, does not provide the underlying cultural changes required to prevent people sharing passwords or other poor data integrity practices. Where an FDA Warning Letter includes data integrity

noncompliance, the agency will usually provide detailed guidance in the Warning Letter on what the organization must do to respond (see FDA Warning Letter Reference: ucm546319).

The wording in many FDA Warning Letters with a data integrity component demonstrates how offers to “fix the problem” without acknowledging its extent or the reason it occurred (for example, “we will write a new procedure and retrain all our staff”) are usually rejected by the Agency. This generally results in worsening the regulatory impact of data integrity noncompliance. Fixing problems without resolving the underlying root cause is analogous to papering over the cracks, rather than standing back and redesigning the methods of working and obtaining significant business benefits.

Looking back, this approach to data integrity remediation (which focuses on gap analysis and risk assessment) is in danger of being similar to the assessment and remediation of computerized systems for 21 CFR 11 compliance, where large amounts of time and effort were expended with little direct business benefit. The problem is that data integrity is a bigger issue than

Part 11, as it covers paper processes as well as computerized systems.

The expectation from the regulatory guidance documents is plain—they want improvements in the current working practices throughout the industry. For example, the UK's MHRA, in their July 2016 guidance<sup>7</sup>, cites:

*"Automated data capture or printers attached to equipment such as balances"* (Line 125)

Figure 1 of reference 7 (MHRA guidance) shows a table supporting use of paper records for what is classed as "Very Simple Systems", with no software.

These systems, such as an analytical balance, need a printer as a minimum for recording the weights of samples and standards. The values from a readout is unacceptable in a regulated laboratory. For other instrument types, such as chromatography instruments, chromatographic printouts are not representative of original data<sup>7</sup>. The principles of this risk-based approach to data integrity are extended further in the MHRA 2018 Guidance<sup>15</sup>, but the table is removed.

Guidance documents also look at hybrid systems. The WHO guidance<sup>9</sup> defines a hybrid system as:

*"... 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."*

The guidance goes further, to say:

- **Use** of hybrid systems is discouraged.
- **Replacement** of hybrid systems should be a priority.

The rationale for moving away from a hybrid system approach is that hybrid systems require two sets of media (paper printouts and electronic records—with associated contextual metadata) to continue to be managed and coordinated

together. The FDA guidance notes that the underlying electronic records are part of complete data and must be retained with any paper printouts. Many laboratories (possibly the majority) continue to use hybrid systems – or define paper printouts as their raw data – and many are unsure how to move forward. FDA Level 2 guidance is clear that paper printouts do not satisfy the predicate rules<sup>16</sup>.

## Impact of data integrity: change current working practices

Many regulated laboratories still follow a workflow based on historical approaches for sample analysis and approval.

This was designed to match historical paper-based systems used in the past (for example, in the last century, where paper was still king), and has resulted in a continued proliferation of hybrid systems. Defining paper as raw data and forgetting the computerized systems that created the records is a major mistake that will result in a regulatory citation.

Section 5.5.4 of the PIC/S Guidance<sup>10</sup>, encourages the design and validation of automated processes to ensure correct and transparent acquisition and processing of data. One of the benefits of a data integrity remediation program is that new solutions should be implemented with the following aims:

- **Paper records:** Move away from paper records as much as possible and implement robust electronic processes with effective system resilience and IT backup.
- **Electronic traceability:** Applications that provide electronic traceability of actions by authorized individuals should be bought (for example, Audit Trail).

- **Calculations:** Move away from performing manual calculations or manually transcribing printed data into other formats (for example, spreadsheets and similar approaches), to implementing calculations that are programmed into the software, such as the instrument data system or other validated software applications. Custom fields within software can be used, but they must be validated.
- **Software algorithms:** Algorithms embedded within software, such as a CDS, are not identical between different CDSs, limiting application of a harmonized AIQ solution, and supporting a case for an independent approach.

Some of the advantages of working electronically are:

- **Electronic data** – Captured at source
- **Metadata** – Content and meaning retained
- **Manual data entry** – Minimized or removed (no transcription checking)
- **Manual calculations** – Replaced with validated automated calculations
- **Networked solution** – Replacing standalone systems
- **Secure control** – Records and data
- **Secure management** – Information
- **Standardized** – Backup and recovery processes
- **Audit trail** – Changes made
- **Electronic signatures** – Where appropriate
- **Paper printouts** – Minimized

In taking an approach for process simplification and improvement, the analytical instrument and associated control software must be adequately specified in the URS. This is necessary

so that the instrument and application can be adequately qualified and validated, respectively. For example, the range of gradient mixing, flow rates, and wavelength ranges, as well as protection of the electronic records generated by the software all need to be specified in the URS.

## Why is AIQ important for data integrity?

In Figure 3, Level 1 of the data integrity model is the right instrument and system for the right job: AIQ and computerized system validation (CSV). This is mirrored in the data quality triangle from USP <1058> (Figure 2). The reason for positioning AIQ and CSV on the bottom is that this is the only layer of either model that ensures correct functioning of the instrument against either traceable standards or calibrated equipment, as well as verification of configured software against testable user requirements. This is the analytical foundation of quality data.

AIQ is essential for the layers above it in both the data quality triangle and the data integrity model. Without assurance of the correct function and operation of the analytical instrument and associated software, the layers above fail to work correctly. The integrity of data generated by the laboratory is compromised. For this, it is important to note that data integrity problems are not just caused by human actions; they can be generated by analytical instruments as well.

To reduce work, consider standardization of instruments, software functions, instrument qualification, and software validation. If implemented, there will be economies of scale, as the same URS will be applicable across several instruments. Data integrity programs within laboratories will drive both

reduction of the number of different ways of working, and the number of systems to qualify and validate, as well as reducing regulatory risk and cost.

The impact on data integrity by either not performing or inadequately qualifying analytical instruments affects the upper layers of the data quality triangle, or Levels 2 and 3 of the data integrity model:

- **Analytical procedure development and validation:** Putting quality into procedure development ensures a robust method that method validation or verification merely confirms. This is a better option than allowing ICH Q2(R1) to determine the parameters to be measured based on the type of procedures, for example, stability indicating or impurity profile. At this point, the chromatographic system suitability test parameters and acceptance limits should be set and verified. The importance of this is discussed in Part 4 of this series of White Papers: *What Does Performance Qualification Really Mean with the 2017 Version of USP <1058>?*<sup>4</sup>.
- **Method transfer:** A robust analytical procedure running on standardized instruments is easier to transfer to manufacturing, a second site, or a CMO/CRO laboratory.
- **Application of the method to routine analysis:** Correct operation of the analytical instrument and any associated software, together with a robust analytical procedure, is essential for ensuring the integrity of the data generated and interpreted in Level 3 of the data integrity model.

The upper layers of both the Data Quality Triangle (Figure 2) and the Data Integrity Model (Figure 3) are method- and application-specific, and assume that

the analytical instrument and associated software is adequately qualified and, where appropriate, the software is validated. However, only the AIQ layer focuses on whether the instrument functions correctly.

## The heart of the matter: your user requirements

To ensure that your analytical instrument and any associated software are qualified and validated respectively, it is essential that the operating parameters of the instrument and the intended use of the software are documented in a User Requirements Specification (URS). The 4Qs life cycle model for the 2017 USP <1058> is shown in Figure 4. The URS requirements for the analytical instrument and the controlling software must be tested and verified during the OQ.

However, this is only part of the picture. The software used in Group C instruments also needs to be configured. As a minimum for GAMP Software Category 3, configuration would typically involve definition of roles with access privileges, where the data are to be stored, and the security settings of the workstation to prevent access to the system clock, data files, and the recycle bin. For more complex software, configuration could be extended to include controls for protection of electronic records, enabling audit trail functionality, and use of electronic signatures. All configuration must be documented in the URS.

For validation of instrument data system software, requirements must be traceable throughout the life cycle, as required by EU GMP Annex 11. The easiest way to do this is through a simple numbering system, as shown in White Paper 2: *How to Comply with the 2017 Version of USP <1058>*<sup>2</sup>.

To ensure that the work is done correctly, a laboratory should take the following measures to ensure that the qualification of instruments reflects the requirements of 2017 USP <1058>:

- **Gap analysis:** Identify differences between policies and procedures for the qualification and validation of analytical instruments/software and 2017 USP <1058> requirements. Some changes will be required to align with 2017 USP <1058>.
- **Periodic review:** During periodic reviews and audits of laboratory instruments, check that the 2017 requirements are documented. These include verification of calculations, control of user-defined programs and software application configuration to ensure data integrity. Where necessary, carry out any remedial activities.
- **URS:** This should be written to be verifiable in the instrument qualification or software validation.
- **Integrate AIQ and CSV:** Create a common approach that addresses both instrument qualification and computer system validation activities.

Where appropriate, it can be useful to include an external perspective to provide advice, consultancy, and resources to undertake some of these activities in a timely manner.

These points are illustrated by a specification for an HPLC detector covering 241–360 nm, and this operating range being qualified in the initial OQ for the instrument. But what happens if a method is required for an operating range that the AIQ does not address?

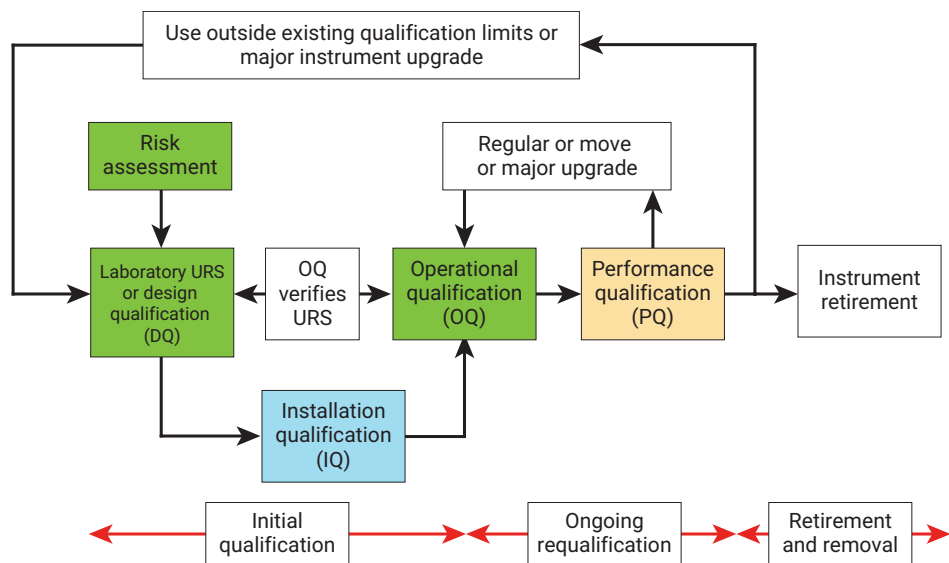


Figure 4. The 4Qs model, showing the relationship between the URS and OQ phases.

- **New method: 239 nm**—A new analytical method requires an operating value of 239 nm. There is not much difference between 241 and 239 nm, is there? Based on USP <621>, wavelength accuracy is  $\pm 3$  nm. Therefore, you may decide to justify that, as 239 nm is within  $241 \pm 3$  nm, it is within the acceptable range. However, if you do not update your URS, it will still state 241 nm as the lower operating range of the detector. Do you think this argument will be accepted by QA or an inspector?
- **New method: 230 or 220 nm**—Assume that the new method requires detection at 230 nm or even at 220 nm. You have a bigger problem, as you are now out of compliance with your URS and the qualified range. Regulatory agencies accept interpolation but not extrapolation. Justifying extrapolation of operating range in an instrument qualification is not advisable. Instead, you will need to submit a change control request,

update the URS, and carry out a supplemental wavelength accuracy test with a suitable wavelength standard.

Three examples are discussed about a scientific approach to instrument qualification.

- **Example 1: Tighter wavelength limit than  $\pm 3$  nm**—A laboratory qualifies their HPLC detectors, but applies a tighter wavelength acceptance criterion for the test than required by USP <621> on Chromatography ( $\pm 3$  nm). Although it is common for HPLC UV-Visible detectors to have a wavelength specification of  $\pm 1$  nm, this is typically based on lamp emission lines and not conditions that are representative of day to day use. It may seem like good practice to apply limits for qualification tests that are tighter than the regulatory requirements, but they should be applied with caution and only where the validation life cycle for the AIQ demonstrates that the limit is applicable. Otherwise, the instrument may fail the tighter limit.

- **Example 2: Range of use**—Assume that a detector or spectrometer has been qualified with a holmium solution down to 241 nm. What happens if a measurement is required at 235 nm—what are you going to do? The new measurement is outside of the qualified range, and regulators do not like extrapolation. A supplemental qualification should be undertaken to cover the new range, as well as updating the user requirements. The OQ needs to be updated to incorporate this change, along with URS and DQ.

- **Example 3: Use of 200 nm or below**—It is not possible to measure the wavelength performance of a UV-Visible HPLC detector at 200 nm or below. There are no reference materials available below the 205 nm peak of the caffeine standard. Therefore, this is a rare example where justification is the only scientific option available (for example, measure the 205 nm caffeine peak and justify why the performance at 200 nm is acceptable). Wavelengths used must be within the specification for the detector.

Instrument performance should be evaluated across the life cycle of use that includes: OQ, PQ, maintenance, and system suitability tests.

## Data integrity considerations for analytical instruments and systems

For Group B and C instruments, depending on the software functionality availability, what should be done to ensure the integrity of the data generated?

This section contains important information on the following data integrity requirements for AIQ:

- Training
- Security and access control
- Technical controls for the operating system
- Electronic records protection and storage
- Printouts

### Training

People performing or reviewing AIQ or software validation work must be trained in data integrity requirements for the work they perform (for example, documented in their training records).

### Security and access control

The following should be in place to ensure that only authorized individuals can access the instrument, and that their work is attributed to a single person:

- **Unique user identities** for all users (for example, unique login and password)
- **Establish and maintain user list** of current and historical users against their user identity. This is the electronic equivalent of a signature list.
- **Never re-use** user identities.

Each user should be provided with these access privileges:

- **Appropriate access privileges** for the task to be undertaken, for example, analyst, supervisor, trainee, laboratory administrator, or IT administrator.
- **Avoid conflicts of interest** where possible, for example, users with administration privileges.
- **For standalone systems** with two or three users, MHRA guidance recommends that users who are administrators can log on with two user types. The first user type should be an administrator with no user privileges, and the second should be a user with no administrator privileges.
- **List:** There must be a list of current and historical users with their user types.
- **User types and access privileges must be documented** as part of the validation documentation, and will be subject to data integrity audits and periodic reviews.

### Technical controls for the operating system

On PC workstations and some instruments, access to the operating system, data in directories, the system clock, and the recycling bin must be restricted to authorized individuals only. Usually, this involves an IT administrator establishing and maintaining Windows security. To prevent introduction of malware and prevent unauthorized copying of records, some organizations will also restrict the use of USB storage devices.



## Electronic records protection and storage

The following should be considered and documented in specification documents used in the validation:

- **Configure the application** to enable electronic record controls (for example, prevent data overwriting, and enable audit trail and reasons for data changes).
- **Enable electronic signatures:** GMP regulations only requires two: performed and reviewer.
- **Ensure secure storage** of electronic records, ideally to secure network locations.
- **Enable effective backup and disaster recovery processes** that are tested and documented.
- **If not undertaken by the application,** devise and maintain naming conventions for records/directories generated to enable easy retrieval of electronic records.
- **Ensure that time and date stamps** are in correct format and unambiguous, for example:
  - HH:MM:SS—12- or 24-hour clock
  - DD MMM YYYY.

## Printouts (if necessary)

Printouts from an instrument or instrument data system should be kept to a minimum. As the regulatory authorities will focus on electronic records, with paper as a secondary source, it is sensible to keep paper printouts to a minimum, for example, only printing a final report. The following should apply:

- **All printouts** must be electronically linked to the underlying electronic records—both the data files and the associated contextual metadata:
  - Data files and run identity
  - Acquisition method
  - Processing method
  - Calculations from and individual values to the reportable result
  - Audit trail entries
- **All printouts** must have adequate document controls, for instance, page X of Y, timed and dated.
- **If electronic signatures are used,** no handwritten signatures are required.
- **For hybrid systems,** each printout needs to be hand-signed by the tester and reviewed by a peer.

## Summary

The integrity of analytical results can be challenged because of data integrity; this includes integrity of the information or the scientific validity of analytical measurements. Analytical Instrument Qualification is designed to address the analytical instrument component of scientific validity by linking the intended use of the instrument with the measurement and evaluation of the instrument performance during AIQ.

The model included within this White Paper shows that AIQ is fundamental to the success of all analytical work performed, including method development and validation, as well as the application of a validated method to the analysis of samples. Performing thorough instrument qualification and software validation ensures that the method and analysis are reliable, and there is lower exposure to possible regulatory action. Ensuring that the instrument continues to perform as expected against its intended use or the URS is the role of PQ, which is discussed in the fourth White Paper of this series: *What Does Performance Qualification Really Mean with the 2017 Version of USP <1058>?*<sup>4</sup>.

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## Appendix 1: Table of example laboratory data integrity nonconformances

No.	Example data integrity citation	Observations	Reference
1	"Out of a list of 62 instruments (SMF), only four were fully qualified. A further five instruments had undergone only DQ, IQ and OQ steps."	<b>Qualification:</b> Inconsistent/Incomplete	<b>EudraGMPD</b> Reference: 35325
2	"Your firm routinely re-tested high performance liquid chromatography (HPLC) samples and deleted previous chromatograms without justification".	<b>Data integrity:</b> File Deletion/Incomplete Data	<b>FDA Warning Letter</b> Reference: ucm527005
3	"Analysts were observed using pre-dated laboratory worksheets".	<b>Data integrity:</b> Contemporaneous	<b>FDA Warning Letter</b> Reference: ucm516163
4	"During the qualification of HPLC system 10, four consecutive tests were performed until a passing result was achieved".	<b>Qualification/data integrity:</b> Repeat work/complete data	<b>FDA 483</b> Reference: 483 Report for FEI 3003882513, 4 April 2016
5	"Numerous data files were found in the recycle bin folder on the computer connected to gas chromatography instruments..."	<b>Data integrity:</b> File deletion/complete data	<b>FDA Warning Letter</b> Reference: ucm528590
6	"In addition, there is no PQ before use and/or a more frequent periodic basis to assure instrument performance."	<b>Qualification:</b> Use of instrument with no PQ	<b>FDA 483</b> Reference: 483 Report for FEI 1000526113, 13 May 2016
7	"The calibration of the Gas Chromatographic (GC) instrument was incomplete. Review of the .... Operational Calibration..... did not include the HS oven temperature, noise and drift, signal to noise..."	<b>Qualification:</b> Incomplete	<b>FDA 483</b> Reference: 483 Report for FEI 3005447965, 21 February 2017
8	"Specifically, your firm failed to qualify the laboratory analytical instruments used for the testing of in-process, finished product and stability samples for all products..."	<b>Qualification:</b> Not done	<b>FDA 483</b> Reference: 483 Report for FEI1000523113, 13 May 2016
9	"This included a gross failure of change management, permitting the use of an unqualified HPLC system".	<b>Qualification:</b> Not done	<b>EudraGMPD</b> Reference: 35704
10	"Our review of audit trail data revealed that your analysts manipulated the date/time settings on your high performance liquid chromatography (HPLC) systems".	<b>Data integrity:</b> Manipulation/Contemporaneous	<b>FDA Warning Letter</b> Reference: ucm563067
11	"Use in quality control a non-qualified chromatographic equipment, with operating faults and with an un-validated computerized management system."	<b>Qualification/computer software validation (CSV)</b>	<b>EudraGMPD</b> Reference: 33564
12	"The GC calibration of system....., used for residual solvent testing of....USP, does not contain raw data such as chromatograms, standards used for calibration and relevant calculations".	<b>Data integrity:</b> Calibration deficient	<b>FDA 483</b> Reference: 483 Report for FEI 3002675552, 18th December 2015
13	"Shredded documents included High Performance Liquid Chromatography (HPLC) chromatograms and a partially-completed OOS form".	<b>Data integrity:</b> Destruction of documents	<b>FDA Warning Letter</b> Reference: ucm538068
14	"Specifically, our inspection revealed your firm did not properly maintain a back-up of HPLC chromatograms..."	<b>Data backup:</b> Not maintained	<b>FDA Warning Letter</b> Reference: ucm448433
15	"Your firm's practice of instrument calibration failure is deficient in that the scope of impact analysis does not extend to all test results generated since the last successful calibration".	<b>Instrument life cycle:</b> (calibration failure)	<b>FDA 483</b> Reference: 483 Report for FEI 3005757050, 29 May 2015
16	"Your quality control analysts used a shared login account to access HPLC systems. This shared account allowed analysts, without traceability, to change the date/time settings of the computer, to modify file names, and to delete original HPLC data".	<b>Data integrity:</b> Shared accounts/attribution	<b>FDA Warning Letter</b> Reference: ucm563067
17	"Our inspection revealed discrepancies between the printed chromatograms and the operational qualification protocol for the High Performance Liquid Chromatography (HPLC) system".	<b>Qualification/data integrity:</b> Printed versus electronic data	<b>FDA Warning Letter</b> Reference: ucm448433
18	"The standards passed system suitability and no limits were established for retention time drift".	<b>System suitability:</b> No limit	<b>FDA 483</b> Reference: 483 Report for FEI 3002806462, 20 January 2017
19	"We observed the same set of sample injections were analyzed on two different Gas Chromatography (GC) systems on multiple occasions..."	<b>Data integrity:</b> Uncontrolled repeat work	<b>FDA 483</b> Reference: 483 Report for FEI 3002808520, 27 January 2017
20	"Assess adequacy of instructions for each method, suitability of laboratory equipment, and competency of analysts."	<b>OOS:</b> Suitability of equipment	<b>FDA Warning Letter</b> Reference: ucm584699
21	"The calculation of signal to noise by... software was not verified for accuracy."	<b>System suitability:</b> CDS calculations not validated	<b>FDA 483</b> Reference: 483 Report for FEI 3000310230, 12 April 2016
22	"You lacked an approved protocol for manual integration or quality oversight of the practice."	<b>System suitability:</b> Manual integration SOP	<b>FDA Warning Letter</b> Reference: ucm585015

23	"Your management acknowledged that employees in your QC laboratories conduct trial HPLC injections"	<b>Data integrity:</b> Trial injections	<b>FDA Warning Letter</b> Reference: ucm495535
24	"During the inspection, your management explained that the laboratory practice was to delete the raw data files once the chromatograms were printed"	<b>Data integrity:</b> File deletion Paper = raw data	<b>FDA Warning Letter</b> Reference: ucm421988
25	"There is no documented evidence that audit trails for electronic data generated from the analytical equipment in the quality control laboratory such as HPLC, GC, or FTIR are reviewed."	<b>Data integrity:</b> Audit trail review	<b>FDA 483</b> Reference: 483 Report for FEI 3003851100, 29 September 2017
26	"Specifically, the HPLCs, GCs, and dissolution units located in the API, formulation (finished dosage form) and stability sample quality control testing laboratories were used outside of the calibration range."	<b>Qualification:</b> Range of use not qualified	<b>FDA 483</b> Reference: 483 Report for FEI 3005029956, 28 April 2017
27	"The following twelve (12) computerized systems and instrument software used in the quality testing laboratory testing laboratory that are currently in use for routine testing have not been validated..."	<b>Software:</b> Not validated	<b>FDA 483</b> Reference: 483 Report for FEI 3002808500, 15 December 2015
28	"Failure of your quality control unit/laboratory to ensure that analytical instrumentation and test equipment used to assure the quality of your APIs has been appropriately qualified and calibrated for their intended use."	<b>Qualification:</b> Range of use not qualified	<b>FDA Warning Letter</b> Reference: ucm236841
29	"No performance qualification (PQ) is required before use to assure the performance of the ***** Spectrophotometer *** series FTIR; only the ...operational qualification is performed."	<b>Qualification:</b> No PQ Performed	<b>FDA 483</b> Reference: 483 Report for FEI 3003519498, 24 May 2017
30	"Your firm has not performed Performance Qualification on the following instruments located in your laboratory" (instrument details redacted in 483)".	<b>Qualification:</b> No PQ performed	<b>FDA 483</b> Reference: 483 Report for FEI 1038960, 4 October 2017

FEI: FDA Establishment Identifier

EIR: Establishment Inspection Report



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