Agilent

Trusted Answers

USP General Chapter <1058>

Compendium

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Introduction

The 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> (in August and December). 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>?[1]
2. How to Comply with the 2017 Version of USP <1058>[2]
3. The Role of Analytical Instrument Qualification in Data Integrity with the 2017 Version of USP <1058>[3]
4. What Does Performance Qualification Really Mean with the 2017 Version of USP <1058>?[4]

The four white papers are included in this compendium for your convenience.

Agilent CrossLab compliance services—helping to maintain a compliant laboratory

Agilent offers a comprehensive set of laboratory compliance services. Services include:

- Instrument and software qualification (IQOQ, OQ and RQ) based on USP <1058> AIQ, and
- Compliance consulting, including validation services such as computer system validation (CSV) based on GAMP5 (Risk Based Approach and V Model), and Part/Annex 11 (Electronic Records and Signatures) for data integrity.

Data integrity is an increasing area of concern for laboratories. In many regulated industries laboratories must demonstrate and document the suitability of analytical instruments and software for their intended use. This focus on compliance extends to how the instrument and software performance is evaluated.

To help our customers ensure compliance in an increasingly stringent regulatory environment, Agilent CrossLab Group has developed an automated compliance solution, designed to support the end-to-end Analytical Instrument Qualification (AIQ) process. The Automated Compliance Engine (ACE) is an electronic, audit-ready qualification solution that addresses Data Integrity and USP <1058> AIQ requirements.

Agilent also offers custom validation services such as computer system validation, audits/assessments, custom procedure writing, and more. These services will help you achieve your data integrity, qualification, and computer system validation (CSV) goals.

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White Paper

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What Has Changed with the 2017 Version of USP <1058>?

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Introduction

This White Paper is the first in a series, and provides information to help laboratories understand the significance of the changes associated with the August[5] and December[6] updates to <1058>, and compares USP requirements between the 2017 and 2008 versions of <1058>[6].

A high-level flowchart showing the sections contained within 2017 USP <1058> is included in the Appendix, along with a detailed comparison of the 2008 and 2017 versions, which is discussed in this White Paper.

A brief history of USP <1058>

First implemented in 2008, USP <1058> originated from an American Association of Pharmaceutical Scientists (AAPS) meeting held in 2003. The resulting White Paper[7] was the basis for USP <1058> and, after public review, it was incorporated into the USP in 2008.

A round table discussion of <1058> was held in 2010, at the AAPS Meeting[8]. Paul Smith was co-chair of this meeting, which included brief presentations followed by an open forum panel Q&A session with invited speakers Bob McDowall (representing a European perspective), Horacio Pappa (representing USP), and Cindy Buhse (representing FDA). Over 250 people attended the two-hour event, which initiated discussions about updating <1058>. The update started in 2012 with the publication of a stimulus to the revision process by Burgess and McDowall, in Pharmacopeial Forum[9]. The stimulus paper proposed an integrated approach to AIQ and computerized system validation (CSV). Proposed updates to <1058> were published in Pharmacopeial Forum in 2015 and 2016 for public comment. The 2017 version of <1058> became effective on 1 August 2017[5], and most of the changes were implemented. The December update[6] included an amendment to clarify wording of the Operational Qualification (OQ) section—a small but significant change.

We now address what has changed in the new version of USP <1058>, and how this impacts laboratories and their approach to AIQ.

The global role of USP <1058>

The USP is the only major pharmacopoeia to have a general chapter on AIQ, so many companies use the approach as a basis for qualifying their analytical instruments. USP <1058> is an important document as it is the only risk-based regulatory guidance on the subject.

USP <1058> is an informational general chapter (providing strong guidance) outlining a scientific and risk-based approach to AIQ, but it does not define the acceptance criteria for specific instrument types, stating[6]:

"Detailed instrument operating parameters to be qualified are found in the respective general chapters for specific instrument types."

The amended update, published in December 2017[6], related to changing the wording of the OQ section to explicitly state:

"OQ demonstrates fitness for the selected use, and should reflect URS".

Recap of USP <1058> Groups A, B, and C

Two of the most useful features of the 2008 <1058> for AIQ were the provision of the Data Quality Triangle (in the Components of Data Quality section) and the classification of instruments into Groups A, B, and C. Both of these features are retained in the 2017 <1058> update, contributing to the familiarity of the general chapter. Separating instruments into groups is an example of risk-based thinking by classification, and is one of the many areas of similarity between USP <1058> and the GAMP good practice guide[10].

Groups A, B, and C are retained in the 2017 <1058>, and the classification is similar (although the wording has been refined):

- **Group A:** *Includes the least complex, standard instruments that are used without measurement capability or user requirement for calibration, such as a magnetic stirrer or vortex mixer. Proper function is ensured by observation, and no further qualification activities are needed for this group.*
- **Group B:** *Includes instruments that may provide a measurement or an experimental condition that can affect a measurement. Examples include a pH meter or an oven. Proper function of instruments in this group may require only routine calibration, maintenance, or performance checks. The extent of activities may depend on the criticality of the application. Generally, these instruments may have firmware, but not software, that is updated by the user.*
- **Group C:** *Comprises analytical instruments with a significant degree of computerization and complexity, such as high-pressure liquid chromatographs and mass spectrometers. All elements of qualification, including software validation, must be considered to ensure proper functioning of instruments in this group.*

The general compliance strategy for each of the three instrument groups can be represented as shown in Figure 1.

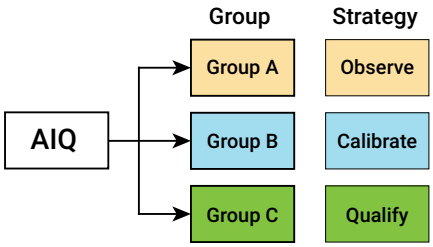

Figure 1. Control strategies for <1058> Instrument Groups.

The role of AIQ in data integrity

Data integrity in regulated laboratories is the focal point in the pharmaceutical industry. It is important to realize the significant contribution that AIQ makes to data integrity. This is best demonstrated by a four layered Data Integrity Model[11]. Figure 2 shows the analytical portion. The four-layer approach can be compared to building a house:

- **Foundation:** Data governance, management leadership, policies and procedures, training, culture, and ethos.
- **Level 1:** Right Instrument and System for the job: Instrument qualification and computer system validation.
- **Level 2:** Right analytical method for the job: Development and validation of analytical procedures.
- **Level 3:** Right analysis for the right reportable result: Analysis from sampling to reporting the result.

The foundation level of this four-layer model consists of the data governance elements, for example, management leadership, policies, procedures and training for data integrity, and an open culture. If these elements are not securely in place in an organization, work in other layers may fail due to data integrity breaches.

Following the foundation, if the analytical instrument, software, or computer system (Level 1) is not *"fit for intended*

use", the *"analytical levels"* 2 and 3 will fail. USP <1058> states the following about AIQ:

"AIQ forms the base for generating quality data"

In the four-layer data integrity model shown in Figure 2, all levels must be in place for secure analytical results. The role of AIQ in data integrity is discussed in more detail in the third White Paper in this series: *The Role of Analytical Instrument Qualification in Data Integrity with the 2017 Version of USP <1058>*[3].

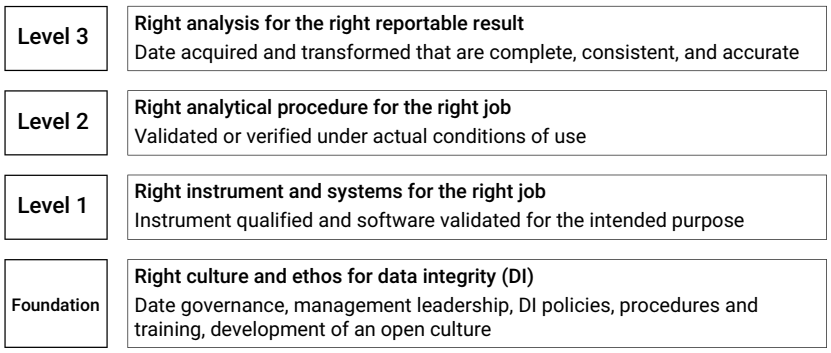

Figure 2. A Data integrity model (reproduced with permission RSC).

Why do we need a new version of USP <1058>?

These are the main limitations with the 2008 version of <1058>:

- **User requirements are not defined:** This means that virtually any OQ protocol could be used to qualify an instrument, even if it did not cover the whole operating range of the instrument.
- **Users are responsible for DQ:** 2008 <1058> places great emphasis on the fact that the design qualification stage is the responsibility of the supplier, but only a user can define their intended use of the instrument to comply with GMP regulations (§211.63).
- **The true role of the supplier is missing:** The supplier is responsible for the instrument specification, detailed design, and manufacture of the instrument, but this is not mentioned in 2008 <1058>.
- **Poor software validation guidance:** Verification of embedded calculations is required by 211.68(b), and users have inadequate responsibility for verification of user-defined programs and validation of instrument application software.
- **PQ requirements were ambiguous:** Differences associated with the role of OQ and PQ testing of instruments was not clear.

One of the major benefits of 2008 <1058> was the introduction of a simple regulatory-aligned, risk-based approach to AIQ, which simplified the requirements for instruments in categories A and B. Before implementation of <1058>, there was an over-reliance on documentation[7]. The 2017 version of <1058> integrates Analytical Instrument Qualification and computerized system validation requirements. This retains all the original benefits while overcoming limitations, and extends the simplification of AIQ into some Group C categories.

What has changed in 2017 <1058>?

In the 2017 version of <1058>, limitations with the original version (outlined above) have been addressed and an integrated approach to AIQ and computerized system validation has been implemented. This integrated approach aligns USP <1058> with GAMP more closely than previous comparisons[10].

Table 2, in the Appendix, shows the main changes between the original 2008 version of USP <1058> and the 2017 version of <1058>. Some of the main changes discussed here are:

- **Example instruments in Groups A, B, and C are deleted:** The 2017 version does not contain a list of example instruments for Groups A, B, or C, as the list was misleading; "fixed" category examples are not aligned with risk-based thinking. The classification is based on the intended use, and <1058> now states: *"the same type of instrument can fit into one or more categories, depending on its intended use"*.
- **User requirements must be documented:** Without user requirements, it is not possible to test the system to demonstrate that it is suitable for intended use. This now harmonizes <1058> with 21 CFR 211.63 for users to define their intended use. User requirements are essential for AIQ.
- **Risk assessment:** Needs to be performed to determine the correct approach to qualifying an instrument (and to which group the instrument is to be assigned).

- **Qualification documents can be combined:** For example, IQ and OQ, or other appropriate qualification phases, could be combined. This harmonizes <1058> with section 2.5 of EU GMP Annex 15 on qualification and validation.
- **Software needs to be specified:** As software is pervasive throughout Groups B and C, it needs to be specified along with the intended use of an instrument.
- **Operational qualification:** Must be linked to User Requirements.
- **Performance qualification:** Differences between the functions of an instrument OQ and PQ are clarified (and the need to perform both).

Protocol documentation option—merging qualification documents

Both the 2017 USP <1058> and clause 2.5 of EU GMP Annex 11 note that, where appropriate, it is acceptable that some documents (for example, IQ and OQ protocols) could be merged into a single document. Note the use of *"where acceptable"*. For a single instrument, this means that both IQ and OQ can be executed under a single set of pre- and post-execution signatures, which can save time compared with executing separate IQ and OQ documents for the same instrument. However, this requires a note of caution, stating that merging a multi-instrument installation into a single document would not be advisable or practicable, as it would prevent parallel execution by two or more service engineers.

Merging AIQ stages such as IQ and OQ into a single document, does not obviate the role of the laboratory user to review and approve the work from the perspectives of scientific soundness and regulatory compliance. For practical reasons, decisions about merging documents are also influenced by the size of the documents.

Impact of changes on the 4Qs model

The impact of the 2017 <1058> changes to the 4Qs model are significant, and are depicted in Figure 3. Software-based V models, such as those based on GAMP, do not translate well to AIQ (unless the instrument AIQ is directly associated with validation of the instrument control software such as CDS). Most instrument-specific qualification diagrams typically present the 4Qs model as a linear process, but in Figure 3, the true V model relationship between key instrument qualification stages are shown.

Two of the changes that have most impact on a laboratory are the need to write a User Requirements Specification (URS) and perform a risk assessment (RA) to determine the group classification. This is shown on the left side of the instrument qualification V model. The consequence of this approach is that the OQ must test the range of use defined in the user requirements, as shown on the right side of the V model.

There is a further impact: does the OQ protocol test the laboratory's actual requirements as defined in the URS, or is a one-size-fits-all qualification used? If it is one-size-fits-all, there is the issue of coverage against the user requirements. We discuss this in the next section.

Impact of change on a qualified instrument

Analytical instruments used in regulated laboratories (for example, Pharmaceutical GxP analysis) must be subject to appropriate change control processes so that the potential impact of the change can be evaluated and approved before being implemented. This must be managed through change control procedures.

Some of the key types of instrument changes that need to be managed are:

- Change of use
- Change to components
- Change of location
- Change of compliance status

Change of instrument use and impact on AIQ

One key change in the 2017 <1058> is that many of the AIQ stages are dynamic and not fixed. For example, if the use of an instrument changes, this may have an impact on AIQ requirements and, hence, compliance status. It is important for the person responsible for an instrument to know the user requirements, so that when there is a change of use, they can assess if the instrument qualification and associated documentation need to be updated. The feedback loop in Figure 3 represents this. For example, consider that there is a specification for the flow rate of an HPLC pump to be between 0.5 and 2.1 mL/min, as shown in Table 1. If a new method is implemented with a flow rate of 1.0 mL/min, there is no issue, as the change is within the limits qualified. However, if a new method that has a flow rate of 2.5 mL/min is used, this has a direct impact on the instrument because it is outside of qualified limits and intended use specification (for example,

the URS). The principles of this apply to all instrument functions specified and tested during the AIQ.

Therefore, for this example of change of use (new method with flow rate of 2.5 mL/min), the following needs to happen:

- URS must be updated
- DQ must be updated (if in a separate document)
- Risk assessment reviewed to see if any changes need to me made
- OQ protocol needs to be updated, approved, tested pre-execution, and reviewed post execution. The extent of testing may just be the pump module or may also include a holistic check of the whole chromatograph—depending on local procedures within the laboratory
- Release for use with the new limits

Change of components

Where there is appropriate information to support the equivalency of components, their replacement does not represent a change to the instrument. Some components are classified as consumables and user-replaceable, while others are typically changed by a certified engineer (or equivalently trained person). The level of testing and certification performed on component parts can vary between companies. Use of lower-cost parts to reduce costs, such as HPLC lamps with no lifetime guarantee, can result in instrument failure and higher overall laboratory costs[12].

Where firmware needs to be updated (for example, standardized for compatibility), this represents a change that needs to be approved through change control. Information released with the instrument firmware can help support the change control process, which needs to define how the change in firmware will be documented and tested.

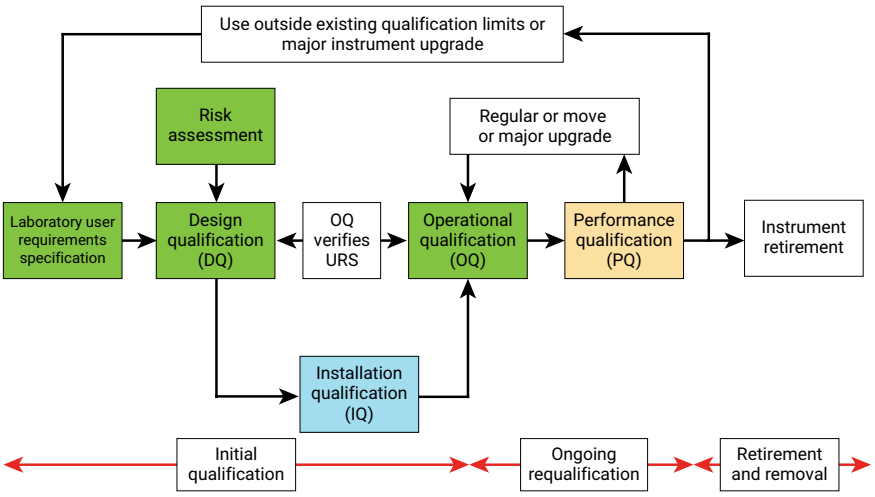

Figure 3. Modified 4Qs model for analytical instrument qualification.

Instrument relocation

"I'm just moving this qualified instrument".

The statement sounds innocuous, but the alarm bells should be triggered in the Quality Assurance department. Changing the location of an instrument (moving, relocating, and so on) typically follows a change control process, unless the instrument is classified as portable (for example, designed to be moved or handheld). When contemplating moving an instrument, stop to think about what may be required from a qualification perspective for:

- A small move along a bench
- Between rooms
- Between buildings
- Between sites
- Between countries

In addition to the need to follow a change control process, with any instrument move, a risk assessment should be undertaken to determine what level of qualification must be performed (for example, how much of the life cycle must be carried out). You should also consider what testing needs to be performed before the instrument is dismantled before shipping. If no premove tests are performed, and the instrument qualification fails at the new location, it may not be clear if the failure occurred during shipping or was present, but undetected, before moving. This will lead to questions about the instrument results before the move, and will require an impact assessment. It is much better to standardize the premove and postmove testing for each instrument type, so that the instrument is tested before the move (safeguarding premove use), and these tests are repeated at the

new location. Typically, premove and postmove testing is in addition to any IQ/OQ/PQ performed at the new location.

Change of compliance status

One question regulated laboratories need to address is the level of requalification required after an instrument repair. If an instrument is repaired, it cannot be put back into use until the performance of the instrument has been tested. For example, if the pump seals on an HPLC pump are changed, the only tests that need to be performed are those specific to the repair (for example, pump flow accuracy and precision). However, this needs to be documented in an appropriate framework to support the decision, otherwise an auditor may expect a full qualification to be performed for every repair, however small. Suppliers and service providers may be able to offer support in the development of such Repair Qualification frameworks, if the laboratory lacks the necessary expertise in this area.

Information associated with the repair can be helpful for the laboratory to evaluate the potential impact of the instrument failure on analytical results. Some laboratories may swap out modules of a system to keep the instrument running. When a prequalified module is inserted into a system, an appropriate level of testing on the system needs to be performed. Without instrument repair information, it can be harder to perform an impact assessment.

From principles to practice

To provide an illustrated example of the thinking necessary to identify user requirements, Table 1 lists example components of a chromatography instrument. The 2017 <1058> says that user requirements for commercial instruments should be minimal, but what does this mean in practice?

When comparing user requirements and instrument specifications with qualification processes, there are many key points to consider:

- **Instrument life cycle documents:** Life cycle information associated with instrument manufacture, such as the design documentation, manufacturing details, firmware testing, and specification testing performed during the manufacturing process and before shipment is detailed. This information is commercially sensitive, and may only be available through supplier audit or confidential disclosure agreement.
- **Manufacturer's specifications:** Instrument specifications are not always defined in the same manner between instrument manufacturers, requiring care when comparing specifications.
- **Qualification limits:** Instrument specifications can be significantly tighter than regulatory requirements defined in sources such as the USP, Ph. Eur., or other pharmacopoeia, which can cause confusion over the limits that should be used during qualification. Generally, the acceptance criteria applied during AIQ should align with the regulatory requirements, as these are what might be challenged during a regulatory audit. Applying limits that are tighter than regulatory requirements can increase the risk that an instrument fails the AIQ. This makes defining the user requirements a critical stage.
- **User requirements:** Historically, some companies may have copied the instrument manufacturer's specifications when defining their user requirements for an instrument. An instrument specification plays a key role in the instrument selection process.
    - **Group A:** URS not required.
    - **Group B:** For simple commercial instruments that are classified as Group B through a risk assessment (for example, a pH meter), it may be permissible to reference the manufacturer's specification in the URS.
    - **Group C:** For complex commercial instruments that are classified as Group C through a risk assessment (for example, HPLC system), copying the instrument specification in the URS should be avoided.
- **System configuration:** The specific components/modules included in the system influence the specification and OQ testing (for instance, the detector type).
- **Detailed specifications:** A full instrument specification for a complex system, such as an UHPLC (for example, an Agilent Infinity II System), exceeds 100 pages when all the module options are considered[13].

The first column of Table 1 contains example analytical methods A, B, and C with which the instrument will be used. Instrument settings associated with these methods are listed for the relevant system components in Table 1. These form the basis for the intended use and, hence, user requirements for the system. In practice, laboratories will have more than three methods, but the principles remain the same.

For example, the HPLC flow rate for the three methods listed ranges from 0.5 to 2.1 mL/min. The instrument specification for the pump is 0.001 to 10 mL/min, so the pump flow requirements for the intended use are within the specification range of the instrument. The pump flow measurements in the OQ need to cover the intended range of use (0.5 to 2.1 mL/min), but it would be meaningless

Table 1. Example of user requirements, associated instrument specifications, and OQ protocol tests.

Use	Module	Setting	User requirements	Instrument specification	OQ Protocol criteria to verify intended use
Method	Pump	Flow	Range (mL/min)	0.001 to 10 Accuracy	Accuracy
A		0.5	0.5 to 2.1	≤1 %	≤5.00 %
B		2.1		Precision RSD	Precision RSD
C		1.8		≤0.07 %	≤0.50 %
Method	Pump	Gradient formation	Range (%B)	0 to 100, in 0.1 increments	Steps 20, 40, 60, and 80 %
A		35 to 75	25 to 75	<0.2 % RSD	Accuracy ≤2.00 %
B		NA (Isocratic)			Linear gradient 100 to 0 % (R^2 ≥0.999)
C		25 to 45			
Method	Autosampler	Temperature	Range (°C)	4 to 40 °C	Accuracy
A		NA (Ambient)	4	4 to 5 °C below ambient	Difference from setpoint ≥–2.0 °C and ≤5.0 °C
B		4			
C		4			
Method	Column oven	Temperature	Range (°C)	Ambient –10 °C to 85 °C Accuracy	Accuracy
A		NA (Ambient)	20 to 55	±0.5 °C	≤3.0 °C
B		20		Stability	Stability
C		55		±0.1 °C	≤1.0 °C
Method	UV Detector	Wavelength	Range (nm)	190 to 600 nm	Caffeine
A		205	205 to 281	±1 nm, self-calibrating with deuterium lines	205, 273 (≤3.0)
B		281			Holmium oxide
C		224			287 (≤3.0)

to test the full flow specification for the instrument. Similarly, one of the intended methods is isocratic, but two are gradient HPLC methods with a combined gradient proportioning range of 25 to 75 %B (for simplicity, binary mixing is assumed for this example). The OQ needs to demonstrate the performance of the gradient pump across the intended mixing range. If the OQ performed by the service provider or supplier does not test the intended range of use, the laboratory will have to perform this instrument OQ testing.

For some instrument parameters, the ability to test the range of use is limited to the availability of reference materials. For example, the wavelength specification for the HPLC UV-Visible detector is typically 190 to 600 nm. However, there are no suitable reference materials available for HPLC UV-Visible detectors below the 205 nm caffeine peak. The detector cannot be tested below 205 nm using caffeine (or any other chemical reference material). Any use of the detector below 205 nm would need to be justified by the laboratory. One of the methods uses a wavelength of 281 nm, which is above the 273 nm peak of caffeine, so extra reference material would need to be used, such as holmium oxide in perchloric acid to ensure that the wavelength range of use (205 to 281 nm in this case) is tested within the OQ.

For temperature-controlled analytical methods, temperature stability of the temperature-controlled instrument component needs to be evaluated, ideally by direct metrology measurement using a suitable calibrated device.

Roles and responsibilities of key players in AIQ

The introduction section of 2017 <1058> includes the clarifying statement:

"The instrument owners/users and their management are responsible for assuring their instruments are suitably qualified."

The following supplementary guidance is provided within the OQ section of 2017 <1058>:

"For OQ test packages purchased from a service provider or supplier, the user must review the material to ensure themselves of the scientific soundness of the tests and compliance with applicable regulations."

The qualification protocol must be approved before it is executed, and the OQ work must be reviewed and approved when complete.

Changes in the Roles and Responsibilities section include:

- **Users:** Users are ultimately responsible for specifying their needs, and ensuring that a selected instrument meets them and that data quality and integrity are maintained.
- **Manufacturers:** Manufacturers are responsible for the design and manufacture of the instruments, and ensuring the quality of the processes used, and for developing meaningful specifications and the conditions under which they are measured for users to ensure that laboratory requirements can be met.
- **Manufacturing section:** Includes suppliers, service agents, and consultants.
- **Technical agreement:** A technical or quality agreement should be in place between the user organization and the manufacturer/service provider that defines the scope of work and responsibilities between the two organizations for any Group B instrument and Group C system.

Merging AIQ and CSV

Before the 2017 version of USP <1058>, AIQ and CSV were considered independent activities by many people. However, with the 2017 edition of USP <1058>, there is an integrated AIQ-CSV approach designed to save time and effort. This integration effort started with the second edition of the *GAMP Good Practice Guide for A Risk-Based Approach to GxP Compliant Laboratory Computerized Systems*[14] in 2012 (ISBN: 978-1-936379-49-1). A paper by Vuolo-Schuessler; *et al.* mapping the new subdivisions of software shown in Figure 4 was published in 2014. It showed great similarity of GAMP software categories with the 2017 subdivisions of Group B and C software[10].

As part of defining an integrated AIQ-CSV approach, the scope of the 2017 <1058> has been expanded, and the sections under software validation have been reworded. Software-specific sections have also been added to the OQ phase of AIQ:

- **Software functions:** This section specifies a requirement to test critical elements of the configured application software.
- **Secure data storage, backup, and archiving:** This section specifies a requirement to test data handling, storage, backup, and archiving.
- **Software configuration and/or customization:** This section specifies that the OQ should be performed using the software that will be used for routine analysis. It also specifies that any software configuration or customization should be performed (and document the settings) before an OQ is performed (otherwise some testing may need to be repeated).

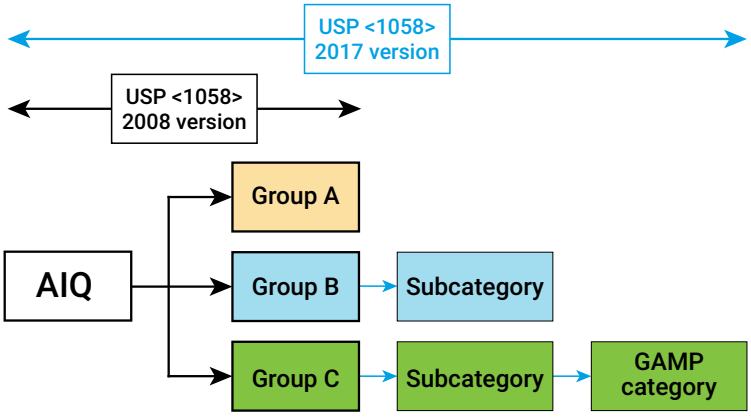

Figure 4. Comparison of the 2008 and 2017 versions of USP <1058> for Software.

To comply with the 2017 requirements, an instrument must be controlled during the OQ using the operating software routinely used with the instrument. For chromatography instruments, for example, the Chromatography Data System (CDS) routinely used with the instruments needs to be used during the qualification work. This approach enhances the data integrity of the qualification work.

However, for software OQ work, unless the application is well understood (for example, a copy is already installed and configured/used within the regulated laboratory), it is unlikely that the software will be configured, as it will be routinely used before the software OQ is performed by the vendor during installation. The laboratory may not have clarified the workflow, user roles, or software functional permissions associated with each role of the intended use at the time of initial installation.

The essential role of software in ensuring data integrity is discussed in the third White Paper in this series: *The Role of Analytical Instrument Qualification in Data Integrity with the 2017 Version of USP <1058>*[3].

Summary

After an initial review, the similarity between the 2017 version of USP <1058> and the obsolete 2008 version may mean that laboratories do not review the USP <1058> changes in sufficient detail. By producing a White Paper dedicated to explaining these changes, this risk should be reduced. After reading this White Paper and considering the changes in the 2017 USP <1058>, current procedures and processes for AIQ and CSV may not fully comply with USP requirements. The first action should be to review your procedures and compare them to the 2017 <1058> requirements. It may be that your SOPs and qualification approaches need to be changed to be fully compliant.

The second White Paper in this series, *How to Comply with the 2017 Version of USP <1058>*, provides deeper insights into the significance of the changes, and offers practical information about compliance.

Appendix

Figure 5 shows the % figure against each of the eight sections of 2017 USP <1058>[6], the approximate size of the general chapter dedicated to each section (based on word count and excluding changes).

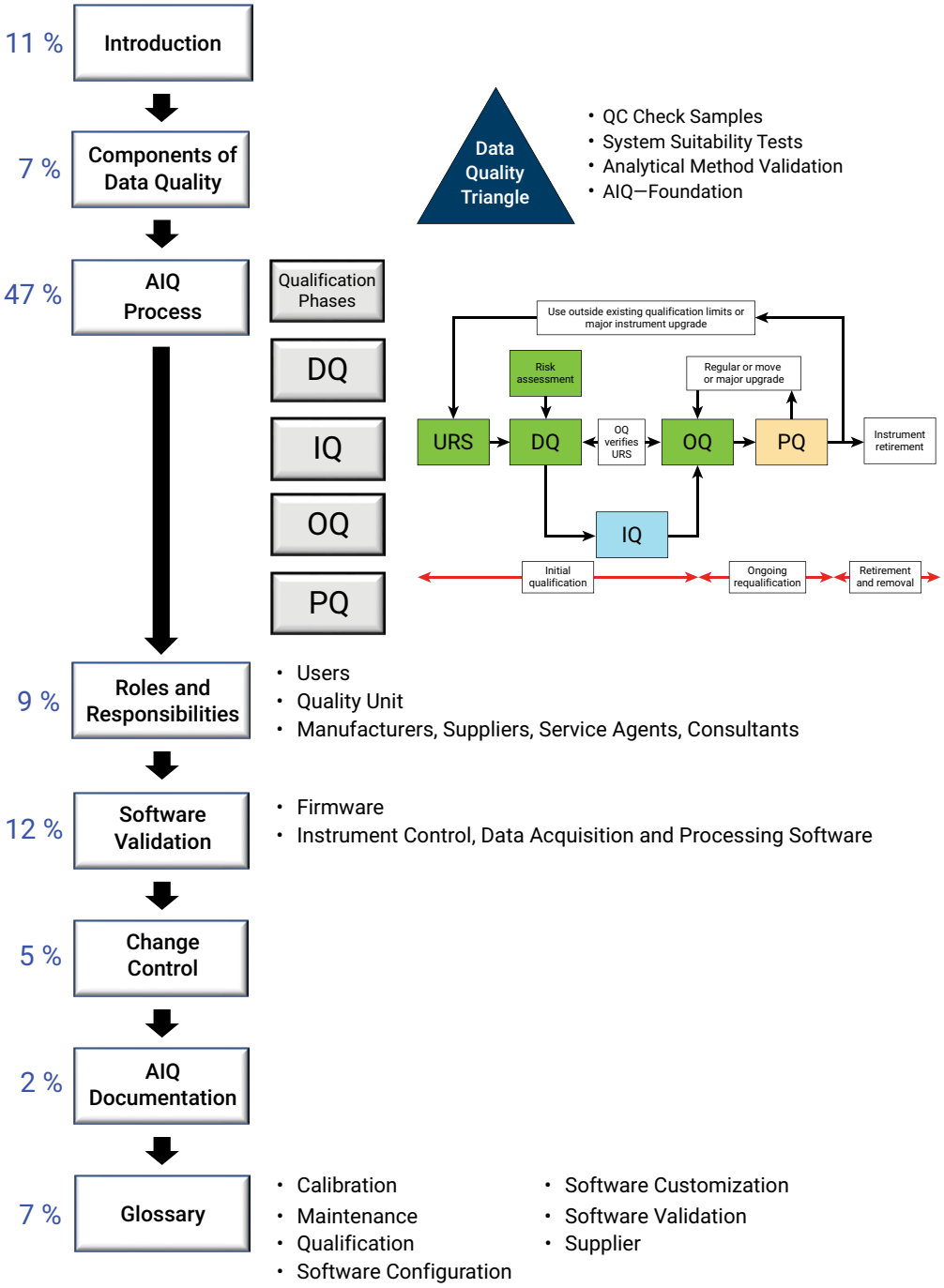

Figure 5. Overview of the eight-section structure of 2017 USP <1058>.

Table 2. Comparison of the 2008 and 2017 versions of USP <1058> on Analytical Instrument Qualification.

Section	USP <1058> 2008 Version	USP <1058> 2017 Version
Introduction		• Expanded introduction • Activities (for example, IQ and OQ) can be merged • Overview description of Groups A, B, and C moved to the introduction • Classification of an instrument depends on the intended use
Validation qualification	Outline of the differences between the two terms	
Components of data quality	• Data quality triangle unchanged • Essentially the same in the two versions	
AIQ Process	**Design Qualification**	
	• Emphasis on supplier to perform this task • Little if any involvement by the user	• Users must define functional and operational specifications and intended use (URS) • Expected to be minimal for commercially available instruments • Demonstrate selected instrument meets user requirements (DQ) • Supplier robust design, development, and testing documentation • Change of use triggers review/update of user requirements
	Installation qualification	
	IQ needed for pre-owned instruments	• Extension of the section to include software installation and IT involvement for interface to a network • Risk assessment for nonqualified instruments
	Operational qualification	
		• Tests must meet requirements in URS • Can be merged with IQ • New section on software functions • New section on software configuration and/or customization • Configure software before OQ testing • Users must review supplier qualification materials • OQ tests refer to instrument-specific general chapters
	Performance qualification	
		• Expended section on practices for PQ, change control and periodic review
Table 1	Timing, applicability, and activities for each phase of AIQ	
Roles and responsibilities		• Expansion of section on Manufacturers to include suppliers, service agents, and consultants • Requirement for a technical agreement between user and supplier
Software validation	Standalone software	• Expanded introduction • Firmware now includes control of calculations and user defined programs • Instrument control software expended section
Change control		• Slimmer and more concise approach to managing change
AIQ Documentation	Essentially the same in the two versions	
Instrument categories	• Description of Groups A, B, and C • Examples of each group	
Glossary		• Definition of seven terms

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White Paper

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How to Comply with the 2017 Version of USP <1058>

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

In 2017, a new version of USP <1058> on Analytical Instrument qualification (AIQ) became effective[5]. The changes introduced in this general chapter are discussed in the first White Paper of this series: *What has Changed with the New Version of USP <1058>?*[1]. In this White Paper, we will look at the impact of these changes on a regulated laboratory, as we discuss some of the practical steps necessary to comply with the changes in the 2017 version of <1058>.

Recap of USP <1058> Groups A, B, and C

Many of the core components that are part of the USP <1058> AIQ framework are included in both the 2008 and 2017 versions. These consist of: the Data Quality Triangle, 4Q qualification phases, and the classification of instruments into Groups A, B, and C. This classification was originally based on:

- **Definition:** Groups A, B, and C which, at a high level, are:
  - **Group A:** Simple apparatus, no measurement capability/calibration needs
  - **Group B:** An instrument requiring calibration
  - **Group C:** An instrument requiring qualification
- **Example instruments:** Were included in Group A, B, and C classification

This approach is the application of risk assessment by classification, where Groups A, B, and C determine the approach/extent of instrument qualification required. One of the original benefits of the 2008 <1058> was to simplify the implementation of instruments in Groups A and B, in particular. Before <1058> was implemented, there was an over-reliance on documentation[6] (for example, a pH meter qualification might have required a 30-page qualification report when it may only require calibration). The inclusion of example instruments for Groups A, B, and C made the classification simple (for example, find the instrument type in the list). However, one consequence of this simplification was that the 2008 <1058> did not address software requirements. For a laboratory balance, for example Group B, the requirement may have been to calibrate the balance and, by implication, the correct operation of the software was verified. The 2008 <1058> did not provide guidance for Group C and Group A apparatus; correct operation was instead verified by direct observation.

Main changes in the 2017 version of USP <1058>

The first White Paper in this series (*What Has Changed with the 2017 Version of USP <1058>?*[1]) concentrated on explaining the changes to USP <1058>. To understand the impact of these changes more deeply, and recognize how to comply with the 2017 <1058>, it is necessary to review <1058> in greater detail.

The main changes in the 2017 version of the general chapter are:

- **User requirements must be documented:** So that a risk assessment can determine the instrument group and the extent of testing. This now harmonizes <1058> with 21 CFR 211.63 for users to define their intended use.
- **Design qualification (DQ):** Users are now responsible for the DQ phase, as only the user knows the intended use of the instrument, and can document why it is suitable.
- **Risk assessment:** Needs to be performed to determine the correct approach to qualifying an instrument and in which group the instrument belongs.
- **Qualification documents can be combined:** For example, IQ and OQ, or other appropriate qualification phases could be combined. This harmonizes <1058> with section 2.5 of EU GMP Annex 15 on qualification and validation.
- **Software needs to be specified:** As software is pervasive throughout Groups B and C, software needs to be specified along with the intended use of an instrument.
- **Example instruments in Groups A, B, and C are deleted:** The 2017 version does not contain a list of example instruments for Groups A, B, or C, as the list was misleading—having fixed category examples does not align with risk-based thinking. The A, B, and C classification is based on the intended use, and <1058> now states *"the same type of instrument can fit into one or more categories, depending on its intended use"*. For example, an ultrasonic bath could be:
  - **Group A** (if used in sample preparation)
  - **Group B** (if a timer or temperature control is used, requiring calibration)
  - **Group C** (if part of a robotic system or where the sonic energy needs to be controlled)
- **Operational qualification (OQ):** Must be linked to user requirements
- **Performance qualification (PQ):** Must be performed

You can read more about these and other changes in the first White Paper of this series: *What Has Changed with the 2017 Version of USP <1058>?*[1].

Impact of the <1058> changes on laboratory procedures

Because so much of the new version of <1058> looks familiar to the 2008 version (for example, data quality triangle, groups A, B, and C, and so on), there is a danger that laboratories underestimate the significance of the changes and risk noncompliance. The key issue is that each laboratory must review and, where appropriate, update their Analytical Instrument qualifications (AIQs), associated SOPs, and related policy documents. It is essential to update the 4Qs life cycle to reflect the

2017 version of USP <1058>, otherwise a laboratory does not meet compliance. Figure 1 shows the 2017 4Q life cycle. This figure is slightly modified from the one presented in the first of the USP <1058> quartet of White Papers, as the User Requirements Specification (URS) and the Design Qualification (DQ) have been merged into a single activity.

An expanded view of the key stages of the 4Qs is shown in Figure 3 in the Appendix, showing how key stages interact to ensure the overall quality of the qualification process.

- User requirements specification (URS)
- Design qualification (DQ)
- Purchase order (PO) and supplier quotation
- Installation qualification (IQ)
- Operational qualification (OQ)

Each of these stages is discussed in more detail in this White Paper, but first the risk assessment must be considered to determine in which USP group an instrument is classified.

An inspector calls

When working in a regulated laboratory, inspections and audits are a fact of life. The third White Paper in this series (*The Role of Analytical Instrument Qualification in Data Integrity with the 2017 Version of USP <1058>*[3]) includes many examples of FDA warning letters, FDA 483 observations, and Eudra GMDP nonconformances associated with laboratory compliance. In the event of an inspection, if you have performed the qualification work internally, you must answer the auditor's questions. For example, is there information available on how the qualification protocol was developed and validated?

Alternatively, if the qualification work has been outsourced to a dependable instrument supplier or service provider,

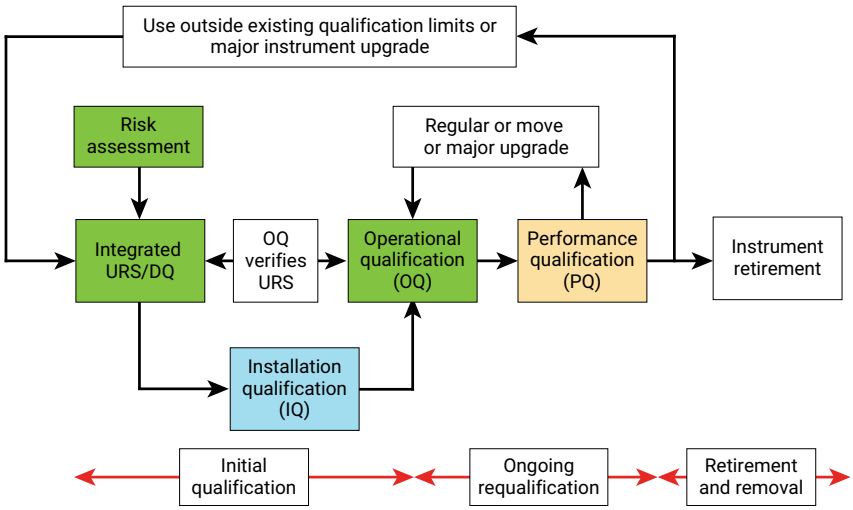


Figure 1. 4Qs Model from the 2017 USP <1058> version showing a merged URS and DQ phase.

you have an organization behind you to help answer any scientific or regulatory questions. Choose your suppliers carefully. Supplier evaluation is an area that forms part of the instrument selection/DQ. The more thorough the supplier evaluation, the more the regulated laboratory will have confidence in the information provided by the supplier. This should be a collaborative relationship.

AIQ—The role of the instrument supplier

During the initial life cycle/implementation of an analytical instrument, the supplier plays two important roles that are key components of the AIQ life cycle:

- Instrument/software quotation
- Instrument specification

Quotation for the instrument/software

Although not mentioned in USP <1058>, the quotation from the supplier and the purchase order for the instrument form the basis for the installation qualification. The components for the overall instrument, which may range from a single item with a power cord to a complex system with a workstation, software, and instrument accessories are an input to the IQ. A packaging note with the instrument delivery should detail what items have arrived on site, and these should match the purchase order or supplier quotation. The packaging material should be designed to protect the instrument during transport and, for precision instrumentation, it may contain accelerometers that detect when the instrument has been exposed to mechanical shock exceeding predefined acceptance limits during transport.

Instrument specification

An instrument specification is a document produced by the manufacturer that represents the functionality, engineering tolerances, range of use, and performance limits for the instrument. For each line of the instrument specification, two of the key components are the range specified for that component and the limits of performance that can be achieved when tested.

The first thing that must be documented is that the range of possible instrument settings listed in the specification

covers the intended range of use (for example, maximum and minimum values for parameters listed in the URS are within the instrument specification range). The second requirement is: does the performance defined in the instrument specification satisfy the user requirements? If the answer to either of these questions is no, the instrument is not suitable for the URS. However, this could also be because the URS is poorly written, specifying inappropriate requirements that cannot be satisfied. Many companies are standardizing their manufacturer/models of analytical instrumentation and software to speed up the AIQ implementation life cycle (and instrument qualification/software validation burden). The DQ document will typically reference the instrument specification document.

Instruments such as HPLCs or GCs are tested against their specification before they leave the factory. Typically, instrument specifications are tighter than regulatory requirements and may be determined under standardized conditions for performance measurement consistency (for example, detector noise and drift tests). However, these conditions may not be the same as those in the laboratory where the instrument is placed, and may also be specified differently between instrument manufacturers (making direct comparison harder). Because of these factors, copying an instrument manufacturer's specification into the URS or the qualification requirements is not advised. Typically, although the specification defines instrument performance under measurement conditions, these are for a new instrument. It may not be possible for instrument performance to be evaluated and guaranteed at the specification limit for the lifetime of the instrument.

The instrument testing performed during the OQ and PQ are designed to satisfy regulatory requirements and not necessarily the instrument specification. The URS also needs to be satisfied.

Writing a URS

Writing a URS can be the worst part of the 4Qs model, as users rarely write these specifications, or when they do, the supplier's specification is sometimes copied verbatim. This must change, as the rationale for a URS is important to understand.

Why is the URS important?

There are two main reasons:

- It is a regulatory requirement for both FDA and EU GMP that the intended use of the instrument and any software must be specified.
- Investment protection perspective means that you get the right instrument for the right job.

From any perspective, the URS defines the range of instrument use, and is at the core of any AIQ and CSV effort. Without a URS, it is not possible to qualify an instrument or validate a computerized system.

As USP 2017 <1058> states[5]:

"The first activity is the generation of a User Requirements Specification (URS), which defines the laboratory's particular needs and technical and operational requirements that are to be met."

The FDA's Guidance for Industry on the General Principles of Software Validation[7] states in section 5.2.2:

"It is not possible to validate software without predetermined and documented software requirements."

Therefore, without documented user requirements, you cannot validate software or qualify analytical instruments.

In the 2017 version of USP <1058>, there is an integrated approach to both AIQ and computerized system validation. For smaller laboratories that may have applied USP <1058> in isolation for AIQ, without other perspectives such as GAMP® for software, this may be a new requirement. Specification of analytical instrument software is now a mandatory requirement and not optional.

Risk assessment: in which group is my instrument?

The first step in AIQ should be to conduct a preliminary risk assessment based on the anticipated use of the instrument to determine to which USP <1058> group the instrument belongs. This is a requirement, and helps the laboratory justify their decisions about <1058> groups (A, B, and C).

- **USP <1058> Group A**
  - Is a risk assessment required?—**Yes** (to document why Group A)
  - Is a URS and DQ required?—**No**
  - The correct operation of the instrument is determined by observation, although some items, such as glassware, will come precalibrated as Grade A. However, your laboratory procedures should document this risk-based approach, and the risk assessment should have an intended use statement at the minimum.

- **USP <1058> Groups B and C**
  - Is a risk assessment required?—**Yes** (to document the group and sub category)
  - Is a URS and DQ required?—**Yes**
  - The URS should include, where appropriate, definition of any calculations performed by the instrument or the software requirements for the instrument data system. When both the URS and DQ have been completed, the risk assessment should be reviewed and finalized to reflect the instrument selected.

When buying another instrument where a URS, risk assessment, or DQ already exists, do these documents need to be recreated?

Where the intended use is the same (equivalent URS), some of the relevant documents can be cross-referenced and do not need to be duplicated. If the existing URS is suitable for the new instrument, the same approach can be used. However, if a laboratory does not have the expertise to make or defend this decision during an audit, it may be a lower risk to repeat the documentation work. It also depends on the detail of a company's policies and procedures. Standardizing and harmonizing AIQ across instruments reduces risk.

What is DQ?

As the 4Qs model originated from manufacturing process validation, DQ is often poorly implemented for analytical instruments because laboratories are not always certain what to do, what to include, or how much detail to provide. This uncertainty was compounded in the 2008 <1058>, which stated that the DQ was the responsibility of the supplier. It is not uncommon to find an absence of DQ documents, poorly implemented DQ documents or, as with URS documentation, DQ documents copied from information supplied by the instrument manufacturer. To understand what DQ is, the first paragraph of the design qualification section from the 2017 USP <1058> is quoted below. The meaning is presented underneath.

"DQ is the documented collection of activities that define the functional and operational specifications and intended purpose of the instrument."

Performing a DQ creates documented evidence that demonstrates that it has been carried out. No documents and no DQ means noncompliance.

An input into the DQ is the laboratory URS that defines an instrument's intended use:

"DQ states what the laboratory wants the instrument to do and shows that the selected instrument is suitable."

This quote demonstrates that the laboratory requirements are compared with the instrument on offer to determine if the instrument meets requirements. This is the qualification or confirmation that the design (as documented in the URS) is met by the selected instrument.

"DQ may be performed by the instrument manufacturer or the user."

In principle, either the supplier or the user can document the DQ. Irrespective of who completes DQ documentation, the user is responsible and accountable for the work. Certainly, the URS should be written in-house for instrumentation (suppliers may be able to help). For software, it can depend on the complexity and range of consultancy services (rather than AIQ services) that the supplier can provide. Detailed implementation of AIQ and software validation requirements can vary significantly between laboratories. Asking a supplier to write a URS or complete DQ documentation can be a challenge without deeper collaboration, as it typically requires in-depth knowledge of the laboratory AIQ policies. It is important to understand that if a supplier or consultant completes the DQ, the laboratory is responsible for its content.

For any URS or DQ documents completed by the supplier (or another organization), the challenge is: how does a laboratory verify that what the supplier has written is correct? The easiest way is by checking the accompanying signature, stating that the instrument, under conditions in the user's laboratory, can achieve these requirements. This forms the contractual basis for an agreement between the supplier and the laboratory:

"It is expected that DQ requirements will be minimal for commercial, off-the-shelf instruments. Verification that the instrument specifications meet the desired functional requirements may suffice."

Meeting minimal requirements is acceptable, but doing nothing for DQ is not an option. The following section explores some simple options for a DQ document.

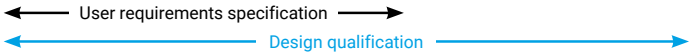
What could a DQ look like?

One of the changes in the 2017 USP <1058> was the ability, where appropriate, to merge documents. Integrating URS and DQ requirements into a single document is one of the possible applications of this approach. Table 1 shows a section of a simple, combined URS and DQ document for an HPLC pump. The URS portion of the document is contained in the first three columns. This includes the requirement number, the requirement, and the operating parameter needed by the laboratory. The design qualification includes the next two columns, outlining the instrument specification and if the instrument meets the laboratory requirements with a Yes or No statement.

This needs to be completed to be compliant with 2017 <1058>. You cannot qualify the instrument unless the user requirements have been documented, as shown in Figure 1 and Figure 3.

Table 1. Differences between a user requirements specification and a design qualification document.

Number	Requirement	User requirements	Instrument specification	Are requirements met?	OQ Protocol criteria (to verify intended use)
P1	Flow accuracy	5 % of set value	≤1 %	Yes	≤5.00 %
P2	Flow range	0.5 to 2.1 (mL/min)	0.001 to 10	Yes	0.5 to 5.0 (mL/min)
P3	Flow precision	±5 %	≤0.07 %	Yes	≤0.50 %
P4	Gradient accuracy	5 %	<0.2 % RSD	Yes	≤2.00 %
P5	Gradient range	25 to 75 (%B)	0 to 100	Yes	20, 40, 60, 80 % 100 to 0 % linear gradient



IQ

The 2017 version of USP<1058> describes the IQ as follows:

"IQ is the documented collection of activities necessary to establish that an instrument is delivered as designed and specified, is properly installed in the selected environment, and that this environment is suitable for the instrument."

Users are responsible for ensuring that the IQ is adequate and covers items such as a suitable location for the instrument. Services must be as specified and any network connection required should be readily available. The IQ will consist of items such as:

- Delivery note and condition of items (including examination of the packaging)
- Site installation requirements
- Environmental requirements
- Services and utilities
- Assembly and installation
- Software installation, network, and data storage
- Installation verification
- Information specified in other documents, such as user manuals and a document of site requirements. These are typically available as PDFs on an optical disk. They should not be copied, but need to be referenced.

Users are responsible for reviewing and approving IQ documents, typically before execution review and after execution approval.

For existing unqualified instruments, the 2017 USP <1058> states the following:

"IQ applies to an instrument that is new or was pre-owned. For any instrument that exists on site but has not been previously qualified, or not qualified to current industry standards, existing documents should be collated and a risk assessment should be undertaken to determine the best course of action."

The quote is self-explanatory. What is not stated is that, if there is no IQ, it is implied that an OQ may not need to be performed. But, the requirements are a URS for the instrument and that the OQ be performed against any instrument control software available.

Align OQ testing with URS requirements

As stated earlier and shown in Figure 1 and Table 1, the 2017 USP <1058> requires that the OQ testing confirms that the URS requirements have been met:

"OQ is the documented collection of activities necessary to demonstrate that an instrument will function according to its operational specification testing in the selected environment. OQ demonstrates fitness for the selected use, and should reflect URS."

For example, Table 1 shows that the requirements for pump flow rate range from 0.5 to 2.1 mL/min with a precision of ±5 %, so the OQ must test the pump over this range, as indicated by the last column of Table 1. However, if the OQ protocol only measures between 0.1 to 0.6 mL/min, the laboratory would be using the instrument outside of the qualified range, and must perform extra testing to supplement the testing performed by the service agent or supplier. It is important to remember that extrapolation in qualification is not accepted by regulatory authorities and auditors, and you need to be prepared to justify or defend this approach. An alternative is that the laboratory performs extra qualification work to supplement the formal OQ testing (for example, OQ testing should bracket the range of use).

USP <1058> and software: risk assessment in an integrated context

The 2017 USP <1058> brings an integrated approach to AIQ and software validation. It is no longer a case of USP <1058> versus GAMP, but is an integrated approach of qualification and validation.

The starting point for this integrated approach is in the URS, which needs to include software requirements. To help this, USP <1058> has subsets of software for instruments in Groups B and C, as shown in Figure 2.

Group B instruments now have three sub classes of firmware:

- **Group Type B1:** An instrument with no in-built calculations or the ability for users to define programs. The instrument requires qualification only.
- **Group Type B2:** An instrument with in-built calculations that must be specified in the URS and verified in the OQ, along with qualification of the instrument. There is no ability for users to define user programs.
- **Group Type B3:** An instrument with the ability for users to define programs. Qualification of the instrument against user requirements. Control of the user-defined programs can be achieved by procedural means for specifying, writing, and testing programs. Security and the ability to change these programs must be controlled.

A similar approach is taken with Group C instruments with application software:

- **Group Type C1:** An instrument to be qualified and nonconfigurable software to be validated. This is GAMP software category 3 (commercially available nonconfigurable product) that cannot change the business process.
- **Group Type C2:** An instrument for qualification operated by configurable software that requires validation. This is GAMP software category 4 (commercially available configurable product) that can change the business process.
- **Group Type C3:** An instrument for qualification operated by configurable software with modules of custom software (for example, macros) that require validation. This is GAMP software category 4 (commercially available configurable product), as previously described, with modules of category 5 custom code.

It is important to understand that a laboratory cannot buy validated software, the laboratory must qualify the instrument and validate the software for intended use.

Therefore, for all types of Group C instruments, the amount of documentation increases as the complexity of the system increases, and could include some or all of the following extra documents:

- **Validation Master Plan** (or Validation Plan)
- **URS:** This will need to be increased to include software functionality such as the platform, compliance, process functions to be performed, IT support, and interfaces to other systems.
- **Configuration Specification:** to record user types with access privileges. Application settings to ensure data integrity.
- **Traceability Matrix** (or Requirements Traceability Matrix)
- **Software Testing:** Integrated with instrument qualification
- **Validation Summary Report**

If writing a macro or other custom software, more validation documents will be required.

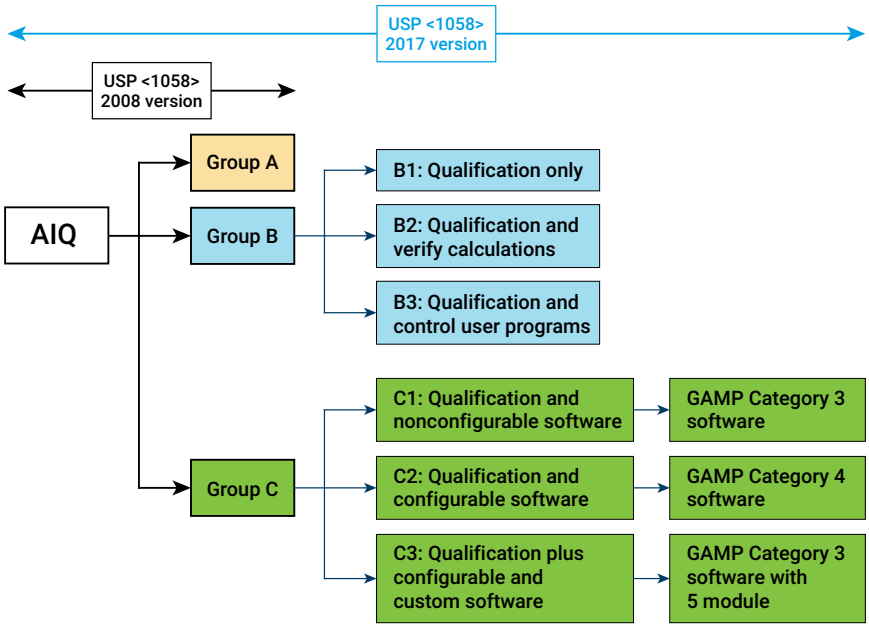


Figure 2. USP <1058> Integrated AIQ and computerized system validation.

Satisfying OQ requirements: standard versus configurable protocols

If a laboratory outsources their AIQ, there are generally two validated approaches that can be found in the marketplace for OQ services:

- **A fixed OQ protocol:** This is a one-size-fits-all approach, which is not designed to be changed. If this protocol meets all the user requirements for the instrument, this approach is acceptable. However, if the standard protocol fails to cover any of the user requirements, such as range of use, there is a regulatory gap that the laboratory must test to fill. This requires more qualification work, which is typically performed by the laboratory. Depending on the workload of the laboratory, the additional qualification work may not be carried out immediately, increasing the time the instrument is unavailable for use.
- **A configured protocol:** This is where a third party takes the laboratory's URS and configures the standard protocol to test all the laboratory requirements in the URS. This is a better approach, as all work is outsourced, meaning a single protocol is executed and no additional work is required from laboratory staff.

PQ

PQ will now briefly be discussed, but if you require a more detailed discussion, see White Paper 4 in this series: *What Does Performance Qualification Really Mean with the 2017 Version of USP <1058>?*[4].

The 2017 USP <1058> defines PQ as:

"PQ is the documented collection of activities necessary to demonstrate that an instrument consistently performs according to the specifications defined by the user, and is appropriate for the intended use."

The problem with this area of the 4Qs model is that few people know what a PQ really is. Most laboratories associate PQ for chromatographic instruments with System Suitability Tests (SSTs); however, from the definition above, PQ relates to the user requirements. The problem with this is that AIQ is instrument-specific and SSTs are method-specific. Are SSTs alone sufficient for a PQ?

"The PQ verifies the fitness for purpose of the instrument under actual conditions of use. After IQ and OQ have been performed, the instrument's continued suitability for its intended use is demonstrated through continued PQ."

PQ testing satisfies two key requirements:

- That the instrument is suitable for use under the conditions of use
- That consistent performance of the instrument can be documented

PQ is conducted post OQ and during time intervals between regular or for-cause OQs. It is essential to demonstrate that the instrument is fit for the intended use (hence the link to the user requirements).

"The user must define the PQ plans, including test procedures, acceptance criteria, and frequency. Preventive maintenance plans and documentation of repairs and other changes are also a necessary part of the overall instrument qualification."

If the range of use of an instrument function is tested in the OQ (for example, column oven temperature or pump flow), there is no requirement to repeat this testing in the PQ. PQ is an integration of planned testing (with frequency and acceptance criteria defined) and all maintenance activities, as well as any change control documented to demonstrate that the instrument is under control.

One issue that is discussed in the fourth White Paper of this series: *What Does Performance Qualification Really Mean with the 2017 Version of USP <1058>?*[4] is if a PQ test should be performed as part of the OQ or immediately after an OQ. The rationale is that this would provide a baseline for all PQ tests to be compared with and allow effective trending.

Summary

This White Paper provides laboratories with deeper insights into the significance of the changes implemented in the 2017 USP <1058> and practical information about how to comply with these changes. This builds on the first White Paper: *What Has Changed with the 2017 Version of USP <1058>?*[1], which focused on explaining the changes.

The third White Paper: *The Role of Analytical Instrument Qualification in Data Integrity with the 2017 Version of USP <1058>*[3] analyzes the role of AIQ in data integrity and why AIQ is important to ensure the integrity and quality of the data generated by all analytical instruments.

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Appendix

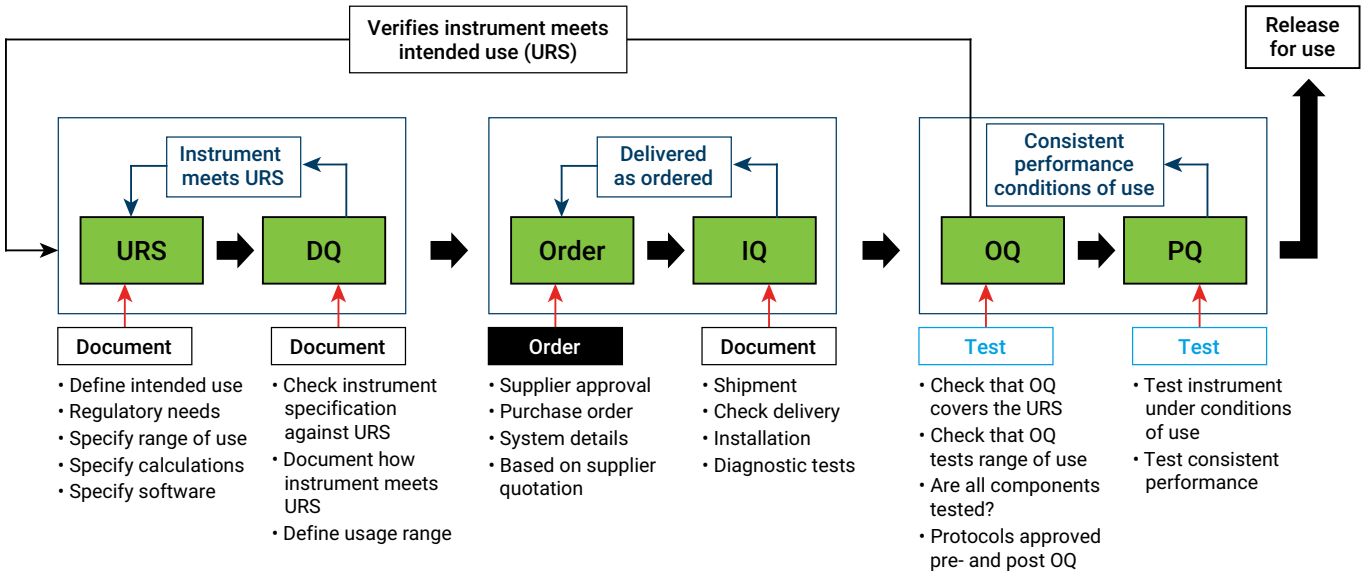

Figure 3. Key stages of the 4Qs model.

White Paper

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

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

In 2017, a new version of USP <1058> on Analytical Instrument qualification (AIQ) became effective[5]. 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>?*[1]. 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.

Recap of USP <1058> Groups A, B, and C

Many of the core components that are part of the USP <1058> AIQ framework are included in both the 2008 and 2017 versions. These consist of: the Data Quality Triangle, 4Q qualification phases, and the classification of instruments into Groups A, B, and C. This classification was originally based on:

- **Definition:** Groups A, B, and C which, at a high level, are:
  - **Group A:** Simple apparatus, no measurement capability/calibration needs
  - **Group B:** An instrument requiring calibration
  - **Group C:** An instrument requiring qualification
- **Example instruments:** Were included in Group A, B, and C classification

This approach is the application of risk assessment by classification, where Groups A, B, and C determine the approach/extent of instrument qualification required. One of the original benefits of the 2008 <1058> was to simplify the implementation of instruments in Groups A and B, in particular. Before <1058> was implemented, there was an over-reliance on documentation[6] (for example, a pH meter qualification might have required a 30-page qualification report when it may only require calibration). The inclusion of example instruments for Groups A, B, and C made the classification simple (for example, find the instrument type in the list). However, one consequence of this simplification was that the 2008 <1058> did not address software requirements. For a laboratory balance, for example Group B, the requirement may have been to calibrate the balance and, by implication, the correct operation of the software was verified. The 2008 <1058> did not provide guidance for Group C and Group A apparatus; correct operation was instead verified by direct observation.

Main changes in the 2017 version of USP <1058>

The first White Paper in this series (*What Has Changed with the 2017 Version of USP <1058>?*[1]) concentrated on explaining the changes to USP <1058>. To understand the impact of these changes more deeply, and recognize how to comply with the 2017 <1058>, it is necessary to review <1058> in greater detail.

The main changes in the 2017 version of the general chapter are:

- **User requirements must be documented:** So that a risk assessment can determine the instrument group and the extent of testing. This now harmonizes <1058> with 21 CFR 211.63 for users to define their intended use.
- **Design qualification (DQ):** Users are now responsible for the DQ phase, as only the user knows the intended use of the instrument, and can document why it is suitable.
- **Risk assessment:** Needs to be performed to determine the correct approach to qualifying an instrument and in which group the instrument belongs.
- **Qualification documents can be combined:** For example, IQ and OQ, or other appropriate qualification phases could be combined. This harmonizes <1058> with section 2.5 of EU GMP Annex 15 on qualification and validation.
- **Software needs to be specified:** As software is pervasive throughout Groups B and C, software needs to be specified along with the intended use of an instrument.
- **Example instruments in Groups A, B, and C are deleted:** The 2017 version does not contain a list of example instruments for Groups A, B, or C, as the list was misleading—having fixed category examples does not align with risk-based thinking. The A, B, and C classification is based on the intended use, and <1058> now states *"the same type of instrument can fit into one or more categories, depending on its intended use"*. For example, an ultrasonic bath could be:
  - **Group A** (if used in sample preparation)
  - **Group B** (if a timer or temperature control is used, requiring calibration)
  - **Group C** (if part of a robotic system or where the sonic energy needs to be controlled)
- **Operational qualification (OQ):** Must be linked to user requirements
- **Performance qualification (PQ):** Must be performed

You can read more about these and other changes in the first White Paper of this series: *What Has Changed with the 2017 Version of USP <1058>?*[1].

Impact of the <1058> changes on laboratory procedures

Because so much of the new version of <1058> looks familiar to the 2008 version (for example, data quality triangle, groups A, B, and C, and so on), there is a danger that laboratories underestimate the significance of the changes and risk noncompliance. The key issue is that each laboratory must review and, where appropriate, update their Analytical Instrument qualifications (AIQs), associated SOPs, and related policy documents. It is essential to update the 4Qs life cycle to reflect 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[13].

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[14].

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.

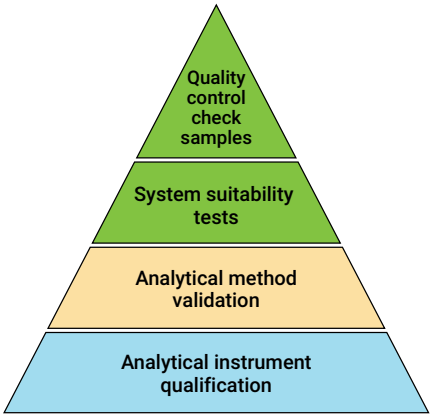

Figure 2. Data quality triangle from USP <1058>.

- 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.

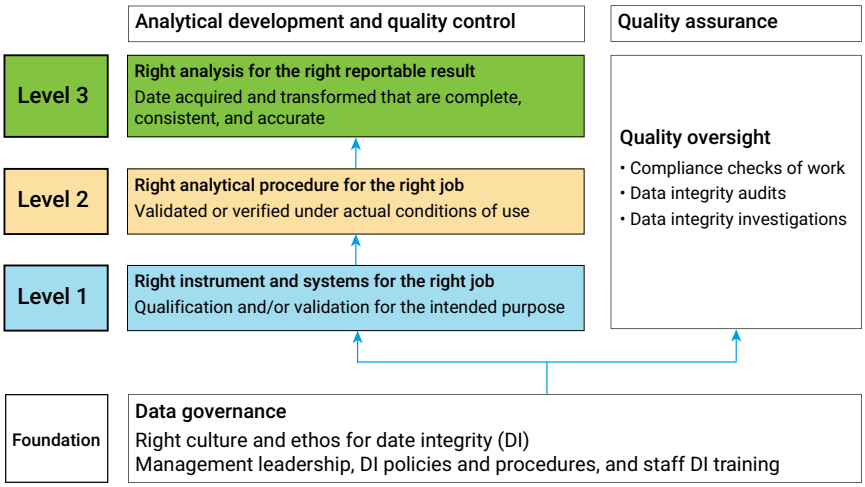

Figure 3. A data integrity model (adapted from CDS2 reproduced with permission RSC).

- **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[7], 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[7]. The principles of this risk-based approach to data integrity are extended further in the MHRA 2018 Guidance[15], but the table is removed.

Guidance documents also look at hybrid systems. The WHO guidance[9] 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[16].

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[10], 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>?*[4].
- **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>*[2].

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?

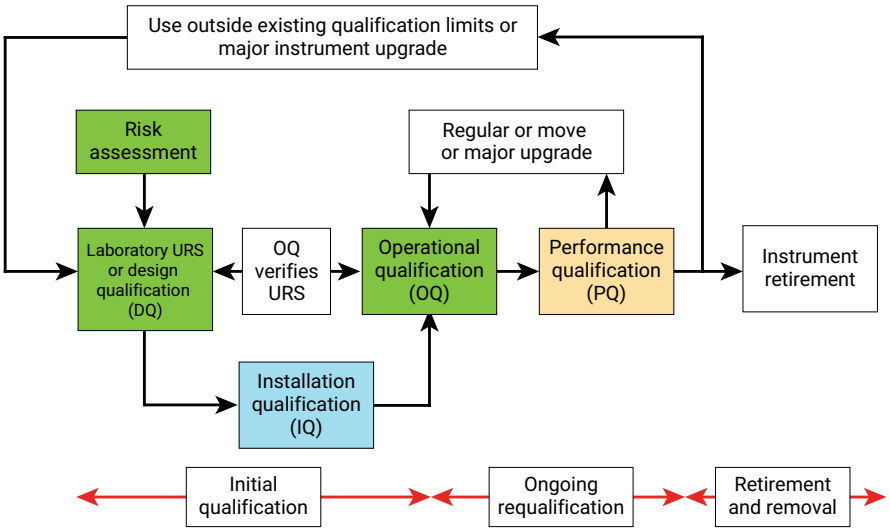

Figure 4. The 4Qs model, showing the relationship between the URS and OQ phases.

- **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 ±3 nm. Therefore, you may decide to justify that, as 239 nm is within 241 ±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 ±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 (±3 nm). Although it is common for HPLC UV-Visible detectors to have a wavelength specification of ±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>?*[4].

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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."*	**Qualification:** Inconsistent/Incomplete	**EudraGMDP** Reference: 35325
2	*"Your firm routinely re-tested high performance liquid chromatography (HPLC) samples and deleted previous chromatograms without justification".*	**Data integrity:** File Deletion/Incomplete Data	**FDA Warning Letter** Reference: ucm527005
3	*"Analysts were observed using pre-dated laboratory worksheets".*	**Data integrity:** Contemporaneous	**FDA Warning Letter** Reference: ucm516163
4	*"During the qualification of HPLC system 10, four consecutive tests were performed until a passing result was achieved".*	**Qualification/data integrity:** Repeat work/complete data	**FDA 483** 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…"*	**Data integrity:** File deletion/complete data	**FDA Warning Letter** Reference: ucm528590
6	*"In addition, there is no PQ before use and/or a more frequent periodic basis to assure instrument performance."*	**Qualification:** Use of instrument with no PQ	**FDA 483** 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…"*	**Qualification:** Incomplete	**FDA 483** 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…"*	**Qualification:** Not done	**FDA 483** 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".*	**Qualification:** Not done	**EudraGMDP** 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".*	**Data integrity:** Manipulation/Contemporaneous	**FDA Warning Letter** Reference: ucm563067
11	*"Use in quality control a non-qualified chromatographic equipment, with operating faults and with an un-validated computerized management system."*	**Qualification/computer software validation (CSV)**	**EudraGMDP** 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".*	**Data integrity:** Calibration deficient	**FDA 483** 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".*	**Data integrity:** Destruction of documents	FDA Warning Letter Reference: ucm538068
14	*"Specifically, our inspection revealed your firm did not properly maintain a back-up of HPLC chromatograms…"*	**Data backup:** Not maintained	**FDA Warning Letter** 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".*	**Instrument life cycle:** *(calibration failure)*	**FDA 483** 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".*	**Data integrity:** Shared accounts/attributable	**FDA Warning Letter** Reference: ucm563067
17	*"Our inspection revealed discrepancies between the printed chromatograms and the operational qualification protocol for the High Performance Liquid Chromatography (HPLC) system".*	**Qualification/data integrity:** Printed versus electronic data	**FDA Warning Letter** Reference: ucm448433
18	*"The standards passed system suitability and no limits were established for retention time drift".*	**System suitability:** No limit	**FDA 483** 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…"*	**Data integrity:** Uncontrolled repeat work	**FDA 483** 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."*	**OOS:** Suitability of equipment	**FDA Warning Letter** Reference: ucm584699
21	*"The calculation of signal to noise by… software was not verified for accuracy."*	**System suitability:** CDS calculations not validated	**FDA 483** Reference: 483 Report for FEI 3000310230, 12 April 2016
22	*"You lacked an approved protocol for manual integration or quality oversight of the practice."*	**System suitability:** Manual integration SOP	**FDA Warning Letter** Reference: ucm585015

23	*"Your management acknowledged that employees in your QC laboratories conduct trial HPLC injections"*	**Data integrity:** Trial injections	**FDA Warning Letter** 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"*	**Data integrity:** File deletion Paper = raw data	**FDA Warning Letter** 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."*	**Data integrity:** Audit trail review	**FDA 483** 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."*	**Qualification:** Range of use not qualified	**FDA 483** 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…"*	**Software:** Not validated	**FDA 483** 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."*	**Qualification:** Range of use not qualified	**FDA Warning Letter** 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."*	**Qualification:** No PQ Performed	**FDA 483** 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)".*	**Qualification:** No PQ performed	**FDA 483** Reference: 483 Report for FEI 1038960, 4 October 2017

FEI: FDA Establishment Identifier
EIR: Establishment Inspection Report

White Paper

Agilent
Trusted Answers

What Does Performance Qualification Really Mean?

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

The changes implemented in the 2017 version of the general chapter[5] were discussed in the first White Paper of this series: *What has Changed with the New Version of USP <1058>?*[1]. In this White Paper, we will look at the impact of these changes on the least understood phase of the 4Qs model: Performance Qualification (PQ).

Evolution of the 4Qs model: impact of 2017 <1058>

The 2008 and 2017 versions of USP <1058> both contain the 4Qs model for AIQ and software validation (for example, DQ, IQ, OQ, and PQ stages). When the need to define a User Requirements Specification (URS) and clarification of the different roles that the OQ and PQ stages have in AIQ are considered, the life cycle model shown in Figure 1 is produced.

This demonstrates the relationship between the instrument qualification stages, and shows that the instrument testing life cycle can be considered as a V model between the DQ, IQ, and OQ stages (see Figure 1).

A key differentiator from the 2017 version of <1058> is that the PQ stage satisfies two different requirements in the AIQ life cycle:

- **Verify** that the instrument is suitable for use under conditions of use.
- **Demonstrate** the continued suitability of the instrument (consistent performance).

The first requirement is satisfied through the inclusion of PQ testing during the initial instrument qualification/release and subsequent instrument qualification testing (for example, periodic and for cause OQ/PQ testing). While the second requirement is fundamental to successful implementation of 2017 <1058>, users must define PQ test plans that include periodic PQ testing in between periodic and for-cause qualification. PQ testing should no longer be considered as running an analytical method on the system. Therefore, even after release for operational use, the PQ phase extends throughout the use of the instrument. This is highlighted with the circle in Figure 1.

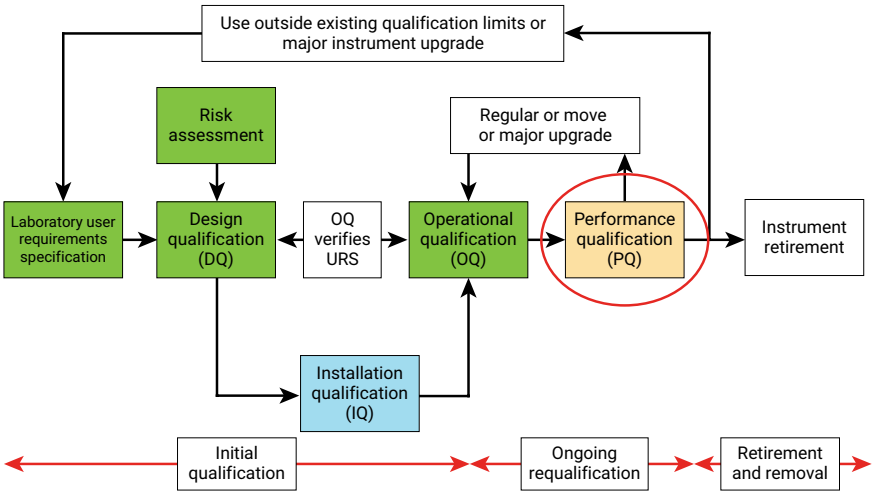


Figure 1. The 4Qs model as a V model.

Historically, when AIQ was first implemented, following application of FDA guidance for manufacturing process validation[6] to laboratory instruments, it was typically performed on an instrument before its initial *"release for use"* (for example, AIQ was perceived as a one-off activity). It is now understood that AIQ is a dynamic process that must be performed throughout the instrument lifetime of use. One of the significant changes in 2017 <1058> is highlighting the dynamic relationship between how an instrument is used and how it is tested (for instance, URS and OQ/PQ testing).

What does USP <1058> say about PQ?

Let us start this discussion by looking at the specific wording of the 2017 version of USP <1058>, which defines PQ[5] as:

*"PQ is the documented **collection of activities** necessary to demonstrate that an instrument consistently performs according to the **specifications defined by the user**, and is appropriate for the intended use."*

This definition is not the same as the 2008 USP <1058> PQ definition, as there is now alignment of the PQ with the laboratory requirements documented in the instrument URS. One of the problems associated with PQ is that few people know what it means. For example, most analytical scientists associate PQ with System Suitability Tests (SSTs) for chromatography instruments.

The reason it is incorrect to define PQ as an SST is that AIQ is instrument-specific and SSTs are method-specific:

"The PQ verifies the fitness for purpose of the instrument under actual conditions of use. After IQ and OQ have been performed, the instrument's continued suitability for its intended use is demonstrated through continued PQ"[5].

The fundamental question many laboratories have for chromatography instruments and 2017 <1058> is this: **are SSTs alone sufficient for a PQ?**

The answer is in the next paragraph of USP <1058>:

"The user must define the PQ plans, including test procedures, acceptance criteria, and frequency. Preventive maintenance plans and documentation of repairs and other changes are also a necessary part of the overall instrument qualification."

Table 1 shows the most common approaches to satisfying PQ testing requirements for HPLC instruments.

Similar approaches to the three options in the table have been used for all chromatography instruments. Each of these choices has apparent advantages and disadvantages. For example, the single largest disadvantage of option 1 is the risk that this approach may be rejected during an audit, while option 3 requires a large number of resources to achieve. Use of a holistic PQ method (option 2) has the advantage that the performance of each instrument can be evaluated in the same way, building up common performance data.

The clarification of PQ requirements in 2017 <1058> means that PQ is not a single activity, but an integration of planned testing (with frequency and acceptance criteria defined), maintenance activities, and checks in operational use, as documented in the instrument logs that will be discussed later. Reliance on only SST results is a weak implementation of PQ for chromatography systems. If your laboratory defines PQ as SST results, and an auditor or inspector challenges this interpretation, what would you do?

Table 1. Example PQ approaches for an HPLC instrument.

	Approach to PQ instrument testing	Comments/Observations
1	**PQ = System suitability tests** *(for example, PQ = SST)*	• Validity of SSTs included in each method? • SSTs are method-specific • Auditor may not accept this interpretation
2	**PQ = Holistic PQ method + SST** *(for example, the same PQ is used for all HPLCs)*	• Simplifies PQ requirements • Builds on SST during use • Justify that PQ testing is representative of use
3	**PQ = Specific PQ method + SST** *(for example, PQ is instrument/use specific)*	• Complicates PQ requirements across a Laboratory *(for instance, specific and different PQ requirements for each HPLC system)* • Builds on SST during use • Instruments dedicated to specific methods

Linking the URS, OQ, and PQ

From the 2017 USP <1058> PQ definition shown earlier, PQ testing must relate to user requirements. The problem is that an OQ typically tests the user requirements directly through traceable standards, metrology measurements using calibrated equipment, and use of appropriate reference materials, designed to test the instrument performance and range of use.

In contrast, a PQ is usually application- or method-based (for example, OQ and PQ test different attributes of system performance, which is why both are required):

- **OQ:** Related to testing the instrument performance under standardized conditions, so that the correct operation of the instrument in the laboratory against the URS can be demonstrated. For example, for HPLC, flow rate accuracy and reproducibility can be measured directly as metrology measurements using a calibrated and traceable digital flow meter. The range of use (for example, maximum and minimum settings) is measured in the OQ phase.
- **PQ:** Addresses the suitability of the instrument under actual conditions of use between repetition of the OQ/PQ cycle. A PQ indirectly measures the laboratory user requirements. For example, flow rate accuracy, and reproducibility can be measured indirectly in a PQ using retention time windows and %RSD of retention time. Because the range of use is measured in the OQ phase, it does not need to be measured in the PQ.

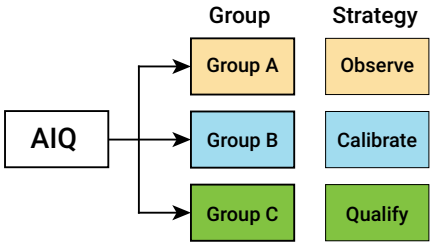
The key issue is that there must be a laboratory URS upon which PQ (and OQ) tests should be based.

The earliest regulatory publication on AIQ is the 1994 paper by Furman; *et al*[7] from the FDA, which includes a discussion of modular versus holistic qualification of chromatographic instruments. The argument was that if the performance of each module or component were within acceptance limits, in principle, the system could potentially fail due to the addition of errors or the system components not working correctly together. The authors proposed the inclusion of an overall system, or holistic test, in the qualification of chromatography instruments, as module testing alone would not detect this.

A holistic PQ test executed after an OQ, or even as part of the OQ, would provide a link between the functional and operational-based OQ and the method-based PQ, as shown in Figure 3.

Instrument complexity and PQ requirements

USP <1058> includes three groups of instrument complexity, with the classification dependent on instrument complexity and use. Generally, the instrument compliance testing strategy for the three groups is:



The first question to ask is—what is the impact of A, B, or C classification on PQ requirements?

- **Group A:** The apparatus are monitored by observation, and do not require user calibration (for example, a nitrogen evaporator or volumetric glassware).
- **Group A—PQ testing requirements:** As long as the observation of successful operation is made under conditions of use, and there is an SOP associated with using the Group A apparatus, there are no additional PQ testing requirements. For volumetric glassware, for example, the SOP would state *"examine before use"*, and discard any unsuitable glassware (for example, damaged or chipped).

Therefore, for Group A (apparatus), no OQ or PQ testing is required, but this decision must be documented in a laboratory procedure.

Groups B and C refer to instruments of increasing complexity. With the 2008 <1058>, laboratories could define the instrument group by looking at the examples provided in 2008 <1058>, but these are not present in 2017 <1058>.

Laboratories must now apply a risk assessment based on intended use to determine if the instrument is Group B or C.

It is also important to understand that compliance with 2017 <1058> is a dynamic process:

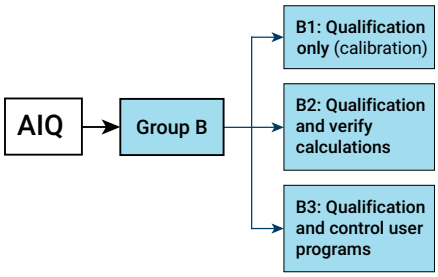
- **More than one category:** An instrument type can be in more than one <1058> category (A, B, or C), depending on use/intended use.
- **Change of use:** May change the group classification (A, B, or C in <1058>)
- **Change of use:** Will change the URS and may change the range of use and qualification requirements

As an example, an ultrasonic bath is sometimes used in sample preparation, to aid the dissolution of the sample. Subject to confirmation (by risk assessment), this would generally be expected to be Group A, with the operation confirmed by observation during use. However, if the ultrasonic bath includes a heater or timer, this may change the group classification. If these functions are used, the risk assessment would identify this, and the classification would change to Group B. The timer and temperature controller must be calibrated against their range of use following an SOP. If these functions are not used, they do not require calibration (for example, because their use is not specified in a procedure). It is unlikely use of these uncalibrated functions can be physically or electronically controlled, so how does a laboratory prevent their use? If they were to be used, this would signify use of uncalibrated instruments (for example, someone uses the temperature controller when it is not calibrated). Compliance would typically be achieved by labeling the status of the instrument (for example, *temperature and timer not calibrated, do not use for compliance work*), training, and documenting in the SOP the instrument use. However, procedural control such as this will not be accepted indefinitely, impacting the user requirements of future instruments being bought (all instruments will need to be designed to satisfy data integrity requirements without procedural control).

The risk assessment also identifies if the firmware of the Group B instrument includes:

- **Calculations:** Built-in calculations (and if they are used).
- **User defined programs:** The ability to create user-defined programs.

For Group B instruments, the risk assessment results in the following extra subclassification:



The extra requirements of B2 and B3 are associated with software testing (see White Paper 2: *How to Comply with the 2017 Version of USP <1058>*[2]). The primary way to document the successful operation of a Group B instrument (rather than test the software) is for a user to calibrate the instrument against an SOP. Depending on the instrument complexity, there may also be maintenance and verification/qualification tests performed by an individual external to the laboratory (for example, service provider or metrology department):

1. **User calibration:** Performed within the laboratory
2. **External maintenance/calibration/ qualification:** Performed by someone independent from the lab

One of the challenges associated with AIQ is that different terms can be used by laboratories and regulators[8]. USP <1058> uses calibration (for Group B instruments) and qualification (for Group C instruments), while the US Code of Federal Regulation (CFR) uses the word *calibration* (for example, 21 CFR 211.68 (a), 211.160 (b)4 and 211.194(d)).

For Group B instruments, the question *"What are the PQ Testing Requirements"*, depends on the answer to the following question:

"Is the routine use of the instrument different from 1 and 2, above?"

If the answer to this question is **No**, then there are no additional PQ-specific testing requirements that need to be included in the PQ test plans.

The instrument life cycle process used in a laboratory needs to document/justify how the testing performed satisfies the OQ and PQ requirements of 2017 <1058>. For PQ, this must include defining PQ test plans, test plans, acceptance criteria, and test frequency. Historically, PQ may only have been considered as a *PQ test protocol*. Addressing this requirement is a laboratory responsibility.

Figure 2 shows the relationship between URS, OQ, and PQ for simple Group B instruments. For simple instruments (for example, a pH meter), daily or point-of-use calibration is the only testing performed. The color-graded box represents the fact that this calibration satisfies both OQ and PQ testing requirements. For more complex Group B instruments (for example, an analytical balance) two kinds of instrument calibration are performed:

- External calibration by a metrology department or service provider tests the range of use and OQ requirements.
- User-performed calibration satisfies PQ testing requirements.

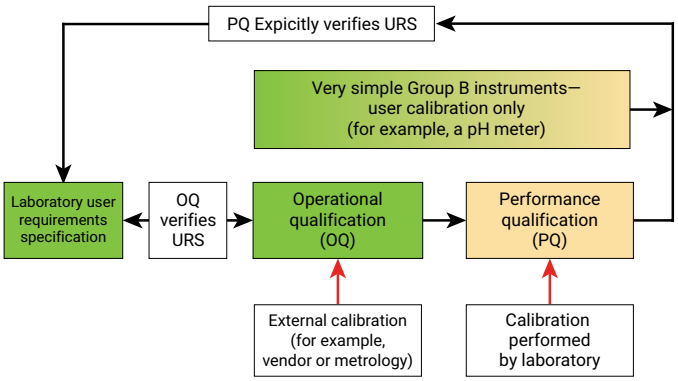


Figure 2. Relationship between PQ and the laboratory URS and OQ for Group B instruments.

For both options, there is a regulatory expectation that laboratories will perform periodic reviews of instrument performance (for example, calibration records).

For Group C instruments, the risk assessment results in the following subclassification:

With more complex Group C instruments, such as an HPLC, there is only an indirect relationship between PQ and OQ tests and the URS because testing involves a separation step that is method-based, as shown in Figure 3.

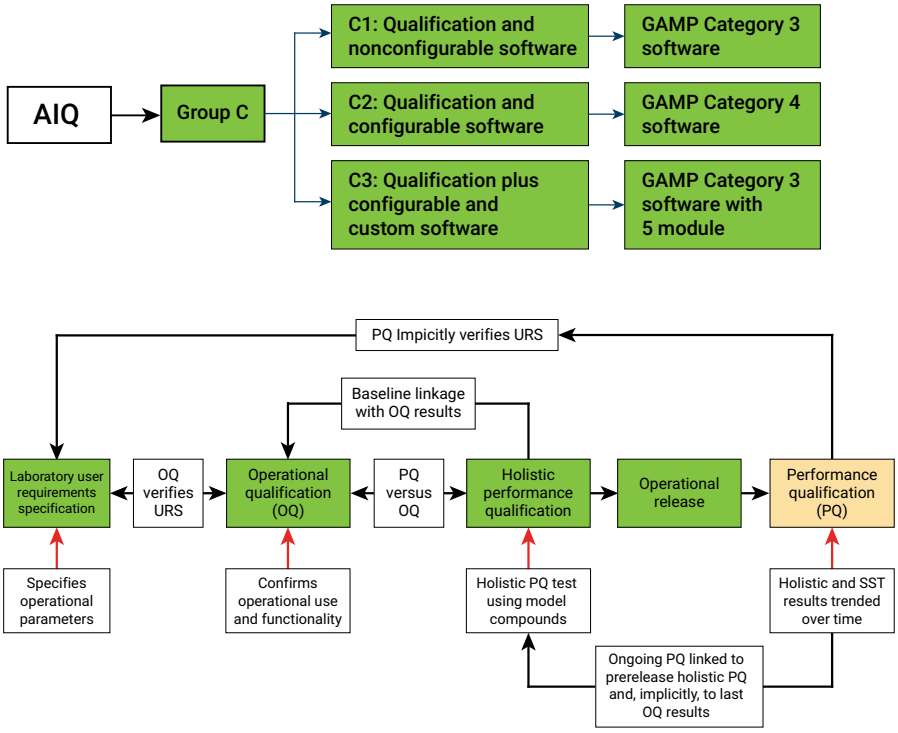


Figure 3. Relationship between PQ and the laboratory URS and OQ for complex instruments.

Risk assessment of an HPLC system—if the system fails, will it be detected?

A pragmatic, but risk-focused alternative way of reviewing the whole AIQ life cycle for an instrument is to consider:

- **Failure:** How might the instrument fail?
- **Detection:** Would the AIQ life cycle/control strategy detect the failure?

These are fundamental risk assessment questions that can be asked of any analytical instrument. However, for an HPLC system, Figure 4 lists some of the most common ways the system may fail. The instrument is shown as four main modules, with common failure modes. This is not an exhaustive list (for example, some of the failures could be subdivided further), and the column is omitted because the aim is to focus on the instrument's qualification.

The conclusion from the original publication[9] was that most of these failure modes would be detected during the OQ, but extra SSTs would need to be implemented to detect some of the other possible instrument failures. The blue text, shown in Figure 4, highlights the instrument failure modes that could be detected by a suitably designed holistic instrument test (PQ).

It is important to understand that this kind of gap analysis (comparing how an instrument might fail and how the failure would be detected through OQ, and SST) and only needs to be performed once for each instrument type. This simplifies performing an impact assessment in the event of instrument breakdown or qualification failure (because the risks have already been considered).

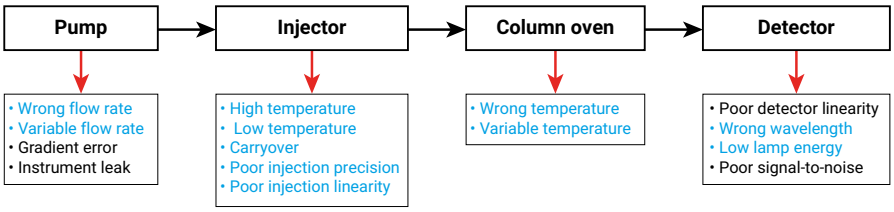


Figure 4. Possible failure modes of an HPLC instrument.

Understanding the scope of PQ

The overall scope of a PQ plan can be seen in Figure 5, and is derived from the explanation of the PQ in USP <1058> presented earlier in this White Paper. The main elements of a PQ should be:

- **PQ plan** covering the scope of PQ activities. Usually, a single plan would be written to cover a type of instrument (for example, HPLC instruments). The plan should have a justification for the approach taken.
- **PQ test procedures** with acceptance criteria
- **Frequency** of test execution

Coupled with this are activities such as routine analysis, repairs, preventative maintenance, and entries in the instrument maintenance and use log. From this discussion, it should be clear that PQ is not just about running chromatographic system suitability tests with each batch of samples.

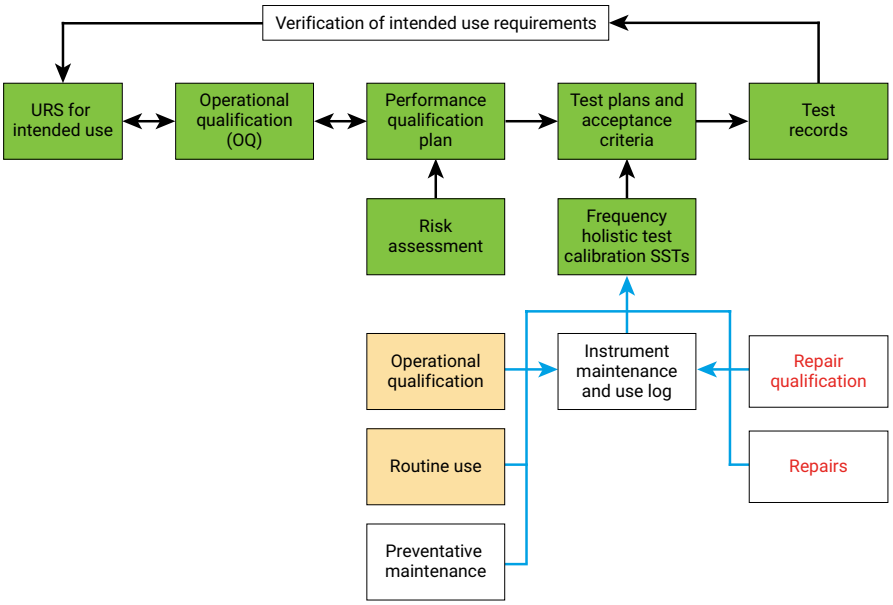


Figure 5. Scope of PQ for an analytical instrument.

Frequency of PQ tests

For chromatographic analysis, a holistic PQ is recommended after the OQ, or should be included in the OQ to link the URS to the OQ and provide a baseline for the remaining PQ. The laboratory needs to determine the frequency of PQ tests and to integrate this into the regular OQ and preventative maintenance cycle. For example:

- Preventative maintenance visit by the service provider
- Annual OQ
- Holistic PQ after the OQ
- Periodic holistic PQ
- SST results gathered and trended each time an analysis is performed to meet the requirements of EU GMP Chapter 6, clauses 6.9 and 6.16, and FDA Guidance for Industry[10]

PQ: linking the layers of the data quality triangle

A modified USP <1058> data quality triangle is shown in Figure 6. Note that only the lowest level of the triangle, AIQ, is instrument-specific, using traceable reference standards and calibrated test equipment. All remaining layers are method-specific. Therefore, if method tests, such as SST and holistic tests, are to be used for the PQ, they must show that the user requirements defined in the laboratory URS are being met each day a test is performed.

A new approach to the development and validation of analytical procedures (based on a life cycle approach) using quality by design (QbD) is the basis of the new draft USP general chapter <1220>, published in Pharmacopoeial Forum[11]. This provides a structured approach to development and validation of analytical procedures, including defining critical parameters that can be monitored by system suitability tests during routine use. This approach will help develop appropriate SST criteria for monitoring and trending instrument performance, and result in more robust analytical methods.

The great advantage of an integrated OQ and PQ approach, linked to documented laboratory user requirements, is that it is easy to defend. The rationale for the qualification approaches taken in both the OQ and PQ phases can easily be traced back to the URS, and the risk assessments undertaken and documented.

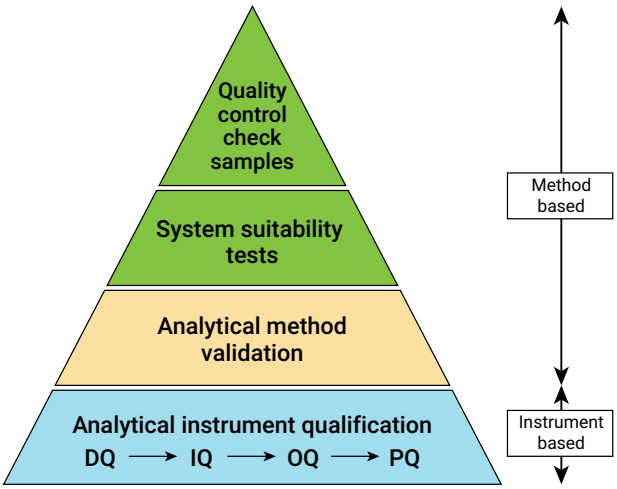


Figure 6. A modified USP <1058> data quality triangle.

PQ Roles and responsibilities

Table 2 shows the roles and responsibilities of people involved in PQ. Most roles are laboratory-based. In principle, an organization outside of the laboratory, such as a service provider or metrology department, could perform a holistic PQ test, but it might be argued by a regulator that this is not fully representative of conditions of use. In fact, PQ is typically a laboratory responsibility and should be carried out by them. When this is carried out on behalf of the laboratory, the people performing the work must receive appropriate training in the PQ testing that is performed.

The key responsibility in Table 2 is that of the subject matter experts to define scientifically sound PQ test acceptance criteria. The basis of a scientifically sound approach is to link the PQ acceptance criteria, derived from method validation, to operational limits derived from the appropriate USP general chapter, for example, for a UV HPLC detector, wavelength accuracy should be ±3 nm rather than ±2 nm from USP <621>, not USP <857>.

Table 2. Roles and responsibilities for performance qualification.

Role	Responsibilities
Process owner	• Accountable/responsible for all qualification work for the instrument • Reviews and approves OQ test plan (or delegates this to specific role in company) • Reviews and approves PQ test plan and test procedures
Subject matter experts	• Write the instrument (and software) user requirements • Reviews and approves the OQ test plan • Writes the PQ plan and test procedures • Defines scientifically sound PQ test acceptance criteria linked to method performance • Executes and documents PQ tests
Quality assurance	• Approves User Requirements Specification • Approves PQ test plan and test procedures • Reviews PQ test data and test results periodically
Qualification engineer	• Performs and documents instrument preventative maintenance and repairs • Performs and documents OQ at defined intervals • May perform holistic PQ test if contracted to do so and appropriately trained

Note: These responsibilities and roles are provided for guidance.

System suitability tests as part of a PQ

Designed to satisfy Pharmacopeia requirements, such as USP <621> or EP 2.2.46, SSTs play a pivotal role in documenting the performance of the chromatography system at the analytical run level. A natural evolution of this is to consider how SSTs can contribute to a PQ test plan.

If SST results are to be used as part of PQ testing of a chromatograph, it is important that:

Method development parameters and acceptance criteria are defined when the method is developed.

- **Method validation** should confirm the suitability of SSTs for performance monitoring and provide traceability between the method validation and the use of SSTs. This should be done to monitor that the instrument is meeting its user requirements during operational use.
- **Trending SST parameters**, as required by EU GMP 6.9 and 6.16 and FDA Guidance for Industry[10]. The summaries of method testing will be part of the overall PQ acceptance criteria.

Many laboratories have implemented *lean initiatives* to reduce potentially unnecessary work. However, this must be balanced with scientific soundness, as required under the GMP regulations, such as 21 CFR 211.160(b), for example:

- **Blank injection removal:** Done to save time, but will limit troubleshooting of a problem, as there will be no chromatogram of the injection of mobile phase. A blank injection can determine if there is any carryover from the autosampler and the level of baseline flatness/noise in the detector response. This can be related back to the user requirements, as discussed later in this White Paper.
- **Control samples:** Similar considerations need to be made for the inclusion of an approved and well-characterized control sample, particularly for impurity characterization. For example, it is not uncommon in a *post lean* laboratory for chromatographic methods not to include a standard to serve as a comparison for the run. Since chromatography is a comparative analytical technique, this could be seen as problematic.

In principle, a risk-based rationale was applied when good chromatography practices were reviewed and cut back. The problem is that relying on leanly designed SST tests means there could be a higher risk of PQ failure and an inability to investigate out-of-specification (OOS) results adequately, or provide scientific evidence that an instrument failure did not affect analytical results (because there is no evidence, depending on what is performed in SST).

Figure 4 shows the common ways an HPLC system could fail. In operational use, some of these failure modes may not be detected, depending on how the instrument is used (for example, lamp emission lines provide a diagnostic wavelength check when a detector

is turned on) and the limits applied to system suitability tests (such as retention time windows).

Care must also be taken when using samples to evaluate the performance of a chromatograph, because recent FDA guidance[12] suggests avoiding sample injections as a means of testing into compliance. All work needs to be included in documented procedures, and the data generated reviewed.

Holistic HPLC PQ test

As part of an overall approach to PQ, there should be a holistic test that can show that the user requirements are still being met. Analytical procedures should routinely be designed to be as robust as possible. However, the principle of a good holistic test is to design an analytical procedure that is sensitive to instrument performance (which is the opposite of normal analytical science). This is the approach used for Performance Verification Testing (PVT) of dissolution instruments, which is universally interpreted as a PQ for these instruments. Ideally, the procedure must use stable model compounds, with simple and stable chromatography to minimize analytical variance from the reference material or use. The performance of the procedure is dependent on instrument performance. The test is performed under actual conditions of use, and for an HPLC instrument, consists of the following:

- **Two stable model compounds:** Well behaved and well separated model compounds that have good peak shape when run in a simple chromatographic system
- **Same absorbance maxima** under test conditions, so that they have the same peak areas when run in the same injection
- **Use a robust chromatography system** with simple organic/aqueous mobile phase
- **Analytical column:** Use relatively short analytical columns to reduce run time for overall PQ test.
- **Prepare standards** in the mobile phase to minimize disturbance when injecting.
- **Prepare standard solutions gravimetrically** to avoid pipetting errors and minimize overall method variance.
- **Use four solution concentrations** (25, 50, 75, and 100 %) containing the two compounds to test that autosampler and detector reproducibility and linearity are prepared.
- **Run sequence:** Consists of a blank, injected once at the beginning of the sequence and at the end of each standard set.
- **Inject each standard** six times.

These overall holistic standards allow limits to be set for:

- Detector reproducibility and linearity
- Autosampler precision
- The combination of the pumping system and thermostatic control of the column

All parameters are measured with the instrument under actual conditions of system use.

Summary

To date, there have been many different interpretations of what AIQ and PQ should contain. The 2017 version of USP <1058> provides some clarification of AIQ requirements and clarification of differences between the OQ and PQ qualification phases. However, as a guidance document, <1058> cannot be prescriptive, and it is a laboratory responsibility to document how their AIQ aligns with, or satisfies, <1058> requirements. Generally, PQ is the AIQ area where there is more diverse interpretation, and this White Paper provides clarification of PQ requirements. To support PQ and deeper understanding of AIQ requirements, Table 2, in the Appendix of this White Paper, lists some of the frequently asked questions related to AIQ and PQ requirements. The changes implemented in the 2017 USP <1058> and implications of those changes need to be understood and acted upon by laboratories, or they risk noncompliance.

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Appendix 1 – Table of frequently asked questions about PQ and AIQ

Question	Answer
Do I need to perform AIQ for all my analytical instruments?	Analytical instruments that are used to make quality decisions within a regulated environment, such as pharmaceutical-testing laboratories, must be suitable for their intended use. Without the ability to demonstrate this, the analytical results may be invalid or challenged during an audit. Performing an AIQ is the best way to address this need. Laboratories should consider and define an appropriate level of qualification for the decisions made on the analytical results, rather than justify why an AIQ is not required. The risk associated with providing any justification for not performing a task is that an auditor/regulator may not fully agree with the interpretation. Where AIQ requirements are not the same (for example, between quality control testing and research and development laboratories), it important to define and manage appropriate levels of AIQ for different kinds of laboratories, rather than applying a universal interpretation (for example, "AIQ is not required for analytical work in laboratory "x" because…").
Can I can ignore USP <1058> because my company does not export to the USA?	Compliance with USP is a requirement for supply of pharmaceutical materials to the USA. Therefore, in principle, a company that does not supply to the USA does not need to comply. However, audits and inspections are frequently about managing regulatory expectations and, as USP is the only major pharmacopeia that includes a chapter dedicated to AIQ, it is influential beyond the USA. USP <1058> provides a valuable framework for AIQ that is simpler to understand than other frameworks, such as GAMP (for example, seven pages versus 352 pages for GAMP 5). Therefore, the contents of <1058> are influential, and should be considered as best practice and a regulatory expectation.

What do I need to include in an AIQ risk assessment?	Performing a risk assessment is now an intrinsic part of USP <1058> compliance requirements. For consistency of risk assessment application, a procedure needs to be defined and documented on this. The procedure should include three stages:
	• Identify if the instrument is group A, B, or C (based on intended use)
	• For all instruments, document how the instrument satisfies the URS
	• For group B instruments, identify:
	  • If any built in calculations are used need to be verified
	  • If any user-defined programs are used need to be validated
	• For group C instruments, identify GAMP categorization:
	  • Group 3, Group 4, or Group 5
	• Verify that the range of use matches the testing/URS or justify use.

Are there regulatory citations for laboratories not performing AIQ?	Yes. Although data integrity has dominated laboratory audits and regulatory inspections in recent years, there is increasing evidence that auditors are continuing to focus in greater detail on laboratory operations, including AIQ. White Paper 3 in this series includes a table of examples of laboratory noncompliance observations from FDA Warning Letters, FDA 483s and the EudraGMDP database (European equivalent to FDA warning letters). See White Paper 3 in References.
Why do I need to write a User Requirements Specification?	User Requirements Specification (URS) was not mentioned in the 2008 version of <1058>. However, the need to document a URS is a fundamental requirement of 2017 <1058>, which states that AIQ or software validation cannot be performed without a URS.
Do I need to perform both OQ and PQ for my analytical instruments?	You must document how your AIQ satisfies OQ and PQ requirements of the 2017 <1058>. Because OQ and PQ test different attributes of the instrument performance, both are required. Details of specific OQ and PQ requirements are dependent on the analytical technology/complexity of the instrument, and the relationship between how the instrument is tested and the conditions of use.

What's the difference between an OQ and a PQ?	OQ and PQ requirements are defined within USP <1058>, but to simplify: **OQ:** Verifies the instrument, satisfies user requirements and range of use **PQ:** Demonstrates the instrument continues to work under conditions of use
My chromatography methods include System Suitability Tests (SSTs), do I also need to perform a separate PQ?	**Yes.** Because SSTs are method-specific, although they contribute to documenting the ongoing instrument performance. On their own, SSTs are not considered fully compliant with PQ requirements of 2017 <1058>. You must document how your AIQ satisfies <1058> PQ requirements and be able to successfully explain this during an audit. This means two key PQ requirements: • That when tested under conditions of use, the instrument is suitable • The continued performance of the instrument is tested and documented
What are the risks associated with using SSTs as a PQ?	Perception of risk is difficult to quantify. The fundamental risk associated with the argument: SST = PQ is that an auditor may not agree with this interpretation or that this interpretation is compliant with USP <1058>. Integrated, well designed AIQ and life cycle processes add to the quality of the analytical results generated and support robust defence of the results (reducing audit risk).
Is PQ a regulatory requirement now?	**Yes.** The 4Q life cycle for AIQ includes PQ as a requirement. This has always been the case, but the 2017 update of USP <1058> has brought this into greater regulatory focus and helped clarify the different roles of OQ and PQ. However, organizations must define in their own policy documents as to how their AIQ processes satisfy USP <1058> requirements, including OQ and PQ requirements.
How often should a PQ be performed?	Users are responsible for PQ test plans. Therefore, it is difficult to give absolute guidance, and users must define the frequency of PQ test plans.
Who is responsible for performing a PQ?	The laboratory is responsible for the quality of all qualification work performed, irrespective of who performs it. Users must define PQ test plans, but other groups external to the laboratory can perform PQ testing as long as testing is approved by the users, and the people performing the work are appropriately trained.
If a user (or service provider) makes repairs such as replacement of HPLC pump seals or the detector UV lamp, what requalification is required?	When an instrument is repaired, the performance of the instrument must be demonstrated before it can be used to perform analysis. This could be a full qualification or only qualification of the system components related to the repair (repair qualification, RQ). To support RQ, an approved procedure must be in place that documents the required qualification after an instrument repair, before it can be returned to use. For example, replacement of the pump seals in the laboratory will not affect the performance of the HPLC detector, and replacement of the lamp will not affect the performance of the pump. For any repairs not documented in the procedure, either a full qualification is required, or a risk assessment must be performed to document and justify the RQ required.
Where do I test the range of use of the instrument?	Testing the operating range of the instrument that is used is a basic compliance requirement of documenting the suitability for use, and one that has resulted in laboratory citations for not being performed. The OQ must test the URS. If the range of use is not tested, there is risk of a regulatory citation. Because of this risk, where the OQ does not test the range of use, extra work is usually performed by the laboratory to supplement the OQ work. It is better to configure the OQ to bracket the range of use, where possible.
Are there any compliance risks associated with "Hot Swapping" components of a system to keep it operational?	Any changes made to an instrument must be made under conditions where the change is documented and approved (for example, change control). The framework a laboratory uses to document and justify the continued suitability and consistent performance of an instrument is important. To perform a detailed impact assessment (where the potential impact of an instrument failure on analytical results is investigated), it is necessary to have appropriate information about the instrument failure. If "Hot Swaps" are used by a laboratory, then the procedure followed should include details of how an impact assessment is performed.
What do I need to ensure that AIQ is compliant with <1058>?	AIQ is a requirement for laboratories. Complying with and appropriating AIQ represents best practice for all analytical laboratories, irrespective of industry. You should: • Understand <1058> requirements and their interpretation • Perform a gap analysis between 2017 <1058> and your AIQ • Check that range of use is documented and tested in AIQ • Prioritize gaps including defining PQ test plans

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Published in the USA, July 16, 2019
5994-1134EN

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