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, 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.

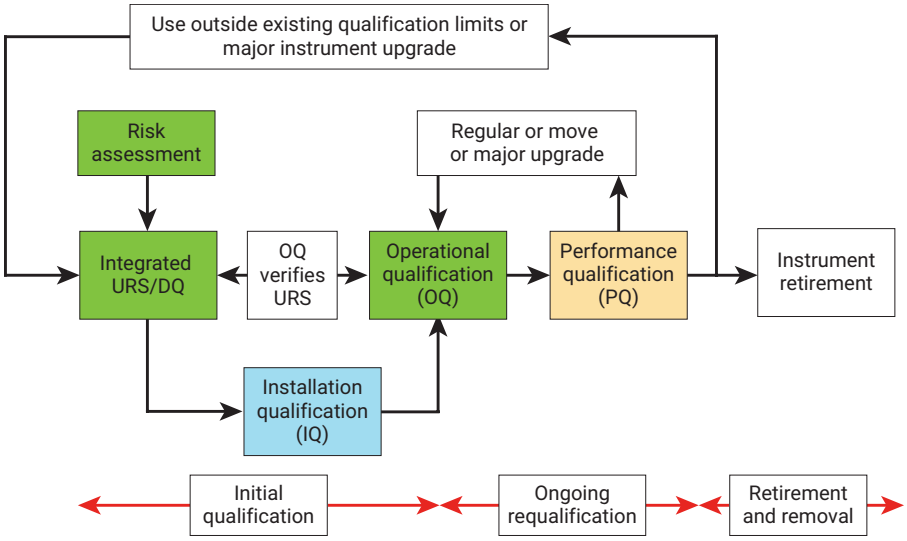


Figure 1. 4Qs Model from the 2017 USP <1058> version showing a merged URS and DQ phase.

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.

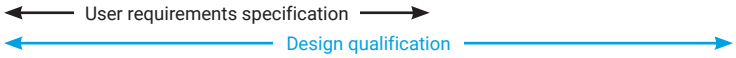
What could a DQ look like?

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.

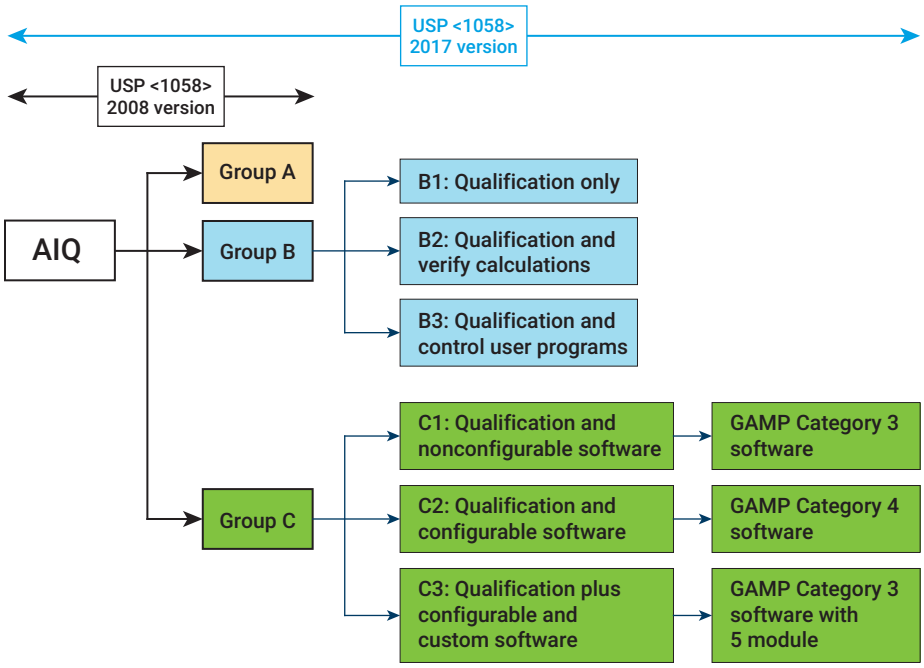


Figure 2. USP <1058> Integrated AIQ and computerized system validation.

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.

References

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Appendix

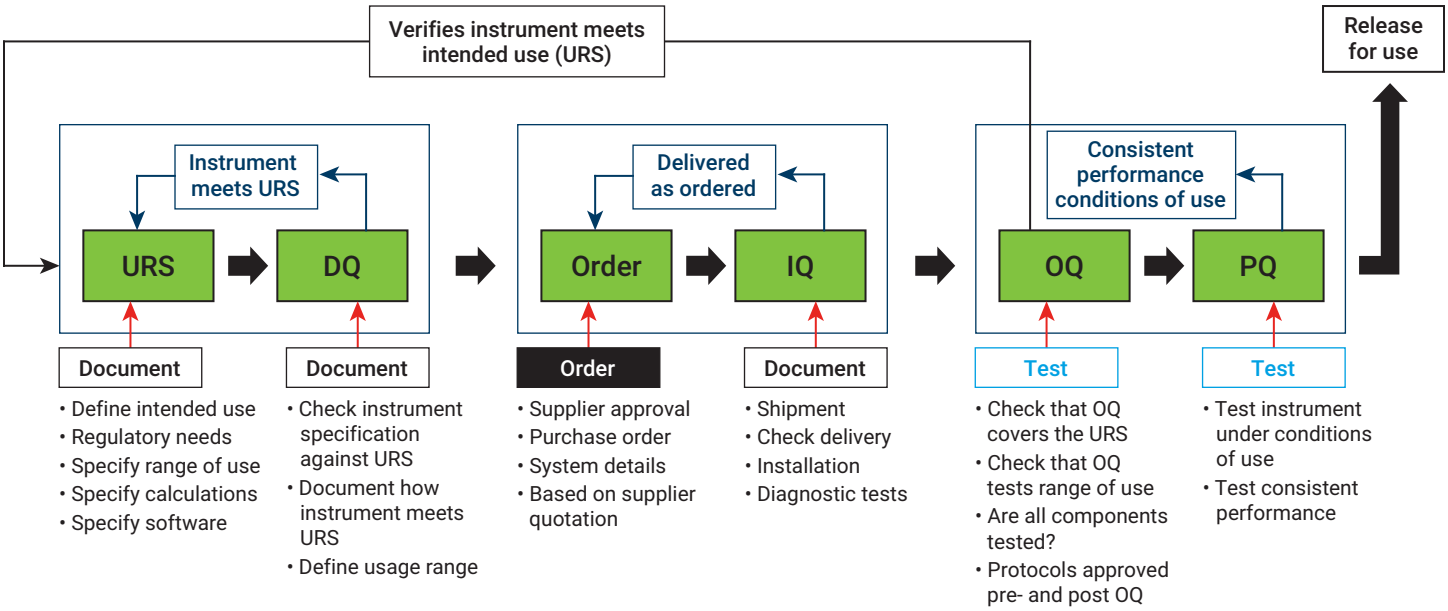

Figure 3. Key stages of the 4Qs model.

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