HOW AGILENT CROSSLAB COMPLIANCE SERVICES INTEGRATE WITH QUALITY SYSTEMS AND REGULATIONS

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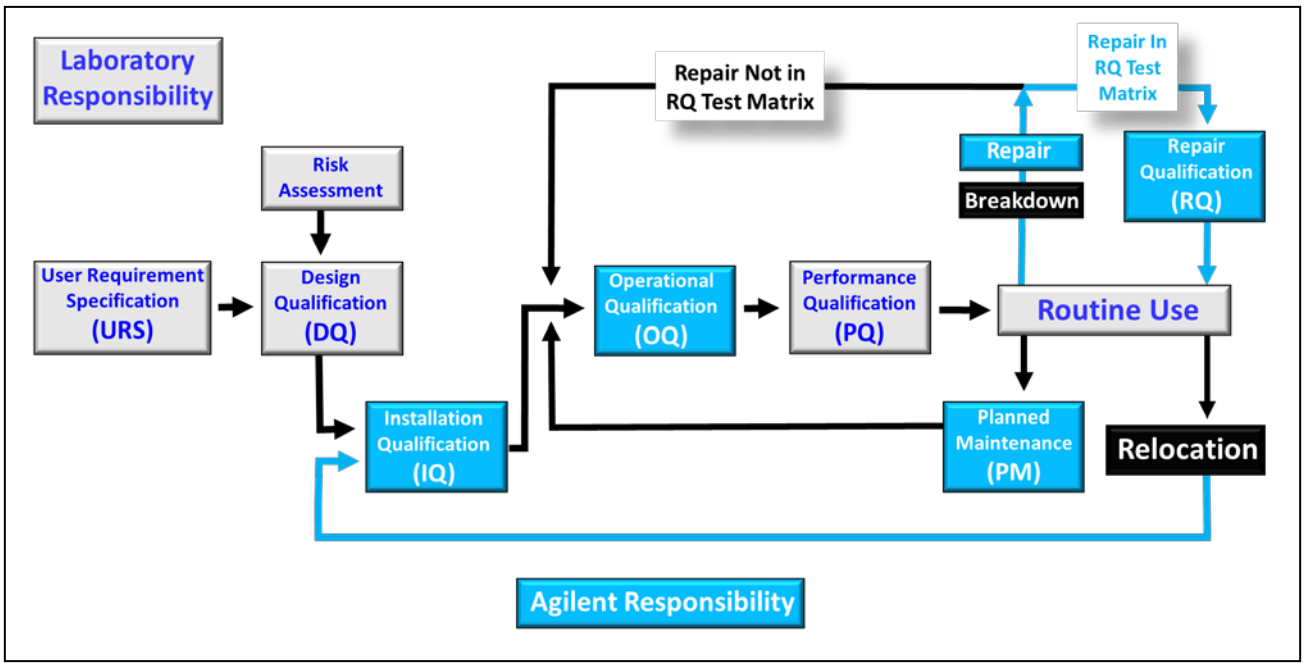
Agilent CrossLab Compliance Services are designed to seamlessly integrate with traditional quality systems used by firms and recognized by regulatory agencies worldwide. Analytical instruments must be suitable for their intended use. This requirement is good science in all laboratories and a regulatory requirement in pharma and biopharma laboratories. A life-cycle process for documenting and testing the suitability of laboratory instruments should be followed and Agilent recommends the life cycle framework defined in USP General Chapter <1058> on Analytical Instrument Qualification (AIQ). USP <1058> defines the governing framework and requirements that need to be satisfied, but the laboratory is responsible for how they satisfy these requirements.

- The United States Pharmacopoeia (USP) is the only major pharmacopeia with a general chapter dedicated to analytical instrument qualification, making <1058> an important global regulatory reference. The information is provided in a scientific, risk-based approach to analytical instrument qualification (AIQ). However, the life-cycle framework contained within USP <1058> is not prescriptive in its implementation, making the embedded scientific and risk-based principles flexible and universally applicable.
- The scientific process followed by CrossLab uses the Agilent's Automated Compliance Engine (ACE) to deliver paperless electronic qualification. The life-cycle stages Agilent perform are highlighted in the life-cycle diagram below. As part of this life-cycle, Agilent can configure the qualification tests performed to align with user requirements.



USP <1058> AIQ Framework

***NOTE**: RQ services, described later in this document, can be added to standard qualification services.*

ACE Workflow and Equipment Qualification Plans (EQPs)

Overview

Within the ACE workflow, the qualification tests, setpoints, and limits are defined in an EQP that can be configured to ensure that testing satisfies user requirements. When the qualification work is complete, an Equipment Qualification Report (EQR) is issued. The electronic workflow used within ACE has significant data integrity advantages over traditional paper or Excel-based qualification protocols, as validated calculations can be performed directly using electronic data such as chromatograms and metrology test values. Several of the instrument life-cycle stages are the responsibility of the laboratory, Agilent can provide compliance consultancy services and documentation which can help customers satisfy these requirements. These additional services are not included in our typical qualification offering.

High-level ACE Qualification Workflow

Standard and User-defined Limits

(Hardware qualifications only)

EQPs are available for download and approval as standard documents with Agilent recommended tests, setpoints, and limits, or they can be electronically configured by approved personnel to align with user requirements and intended range of use requirements. The degree of configuration depends on the analytical technology, but most EQPs can be configured to some degree, and one feature that can typically be changed is test limits.

EQPs are designed to be configurable (dependent on the analytical technology and standard requirements), but including additional tests or setpoints can impact the qualification time and associated cost. If a test limit is changed, ACE includes the capability to report results against the Agilent approved limit and any customer required limits (that is, both can be reported simultaneously).

If a user-defined test limit is more stringent than an Agilent recommended limit, Agilent makes no guarantee or obligation regarding the instrument passing the tighter test specification requirements. It is important to appreciate that tests performed under conditions of use (that is, to satisfy pharmaceutical monograph and application requirements) can have different limits than those defined in the OQ. It is the continuum of the combined OQ, PQ, and any point of use testing performed each time the instrument is used that together satisfy regulatory requirements.

User Requirements Specification (URS)

The purpose of user requirements is to document the intended use of the instrument within the life-cycle process and quality management system (QMS) being followed. Therefore, the URS is a customer / laboratory responsibility. Defining user requirements is often used to guide the customer in instrument selection and is stated as the first activity that should be followed in <1058>. The URS is important for two main reasons.

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

Qualification protocols should test the instrument against any limits or specifications listed in the URS, which should document the intended range of use. Depending on the instrument complexity and how it is classified, a separate URS document may not be needed, but the URS requirements of the <1058> framework must be satisfied. A separate URS is almost always recommended for computerized systems.

An instrument performance specification is a product of the instrument development process by the supplier. It typically documents the performance the instrument can achieve. The URS should be based on intended use of the instrument and not the instrument specification. Additionally, if the intended use of a system changes, this may trigger a need to review the URS and associated qualification testing (for example, to ensure range of use is tested if used with a new analytical procedure).

Agilent offers compliance consultation services and documentation that can help customers address URS requirements.

Design Qualification (DQ)

The main function of the DQ stage of the laboratory instrument life-cycle process is to document why the selected instrument is suitable. Typically, this includes consideration of the instrument specification, how the instrument will be qualified, and the QMS followed by the instrument manufacturer. All together, these confirm that instrument performance is capable of satisfying user requirements. Depending on laboratory instrument life-cycle policy or SOPs being followed, instrument requirements and the relationship between the URS and DQ stages may vary – but as long as the <1058> framework principles are satisfied, this is not a problem, as it is left to each laboratory to justify and document its specific approaches.

The responsibility for satisfying DQ requirements primarily lies with the laboratory, with support from the supplier.

Agilent's approach to satisfying DQ requirements of USP <1058> includes the following.

- All Agilent hardware and software laboratory products, including the ACE software used to deliver qualification services, are designed, manufactured, and tested according to Agilent internal quality life-cycle development procedures.
- Certificates of Agilent testing, validation, and conformance to standards are provided with new Agilent instruments and similar certification can be provided for ACE software.
- Agilent is capable of installation, support, preventive maintenance, on-going qualification, and re-qualification after repair and user training worldwide.

Agilent offers a compliance consultation service that can help customers with DQ documentation.

Installation Qualification (IQ)

The main functions of the IQ stage are to document that laboratory is suitable (for example, critical systems typically include a site inspection / checklist), that the instrument is installed correctly in the environment, and IQ checks such as module start up are completed. IQ is provided and automated by ACE, which collects, checks, and tests Agilent hardware and software products for the following.

1. Purchase Order Details: Allows the customer to verify that the instrument being qualified matches their design requirements (if available) and purchase order.
2. Preparation and Installation Details: Gathers and records information about preparation and installation documents.
3. Documentation: Gathers and records information about reference and user manuals for initial installations.
4. Product Quality Assurance Details: Collects and records certificates and other forms that verify that the vendor has developed and built the product according to internal standards.
5. Startup: Verifies that all modules/components start up properly.
6. Installation Verification (software only): Verifies the correctness of all installation-related files.

Operational Qualification (OQ)

The main function of the OQ stage is to evaluate and document instrument performance at the intended operational range of use. OQ protocols should include a mix of metrology, functional, and operational tests. ACE qualification protocols include information about the test description and rational, setpoints, and the limits (acceptance criteria) for each technique, category, and instrument configuration.

OQ is provided and automated by ACE. ACE checks and tests for Agilent hardware and software products include the following.

- Metrological tests such as flow, temperature, pressure, and so on that ensure that the system is performing within Agilent (or user) specifications.
- Qualification results are reported in the EQR, which can include details of all test certificates, standards, and training information for the engineer performing the work. (Note that the EQR can be configured to customer requirements.)
- System or "holistic" tests verify the combined functions of the various system components
- The qualification testing can be configured to ensure URS requirements, such as range of use are tested.

For software qualification, the OQ consists of automated diagnostics regression testing and verification of the software installation. This supports continued use of the software in regulated environments (at install and as part of supporting periodic review).

In line with regulatory requirements, the EQPs should be approved before work is performed and the EQR should be reviewed and approved when the work is complete (as illustrated in Figure 2). The EQR contains all the raw data, results, and relevant information and attachments for complete compliance and traceability.

Mechanical Qualification (MQ)

(Dissolution systems only)

The main function of the MQ stage is to document that the mechanical performance of the instrument meets specifications and is functioning properly.

Performance Qualification (PQ)

The main function of the PQ stage is to document that the instrument is fit for purpose under conditions of intended use and to create an approved framework that ensures the instrument continues to perform as required. Because instrument range of use is tested within the OQ stage, it is usually not necessary to test this during PQ. It should be noted that requirements for instrument maintenance and repair fall within the PQ life cycle stage within the USP <1058> framework, as they are components of ensuring the continued performance of the instrument.

The customer is responsible for satisfying PQ requirements. (NOTE: Agilent can provide a PQ for Dissolution systems only.)

It is important to note that PQ is a lifecycle activity and not a one-time event. PQ tests may include activities such as method validation or system suitability tests (SST), but in Agilent's opinion, SSTs contribute towards ensuring continued performance of the instrument (that is, PQ testing), but do may not fully satisfy <1058> PQ requirements.

Repair Qualification (RQ)

After an instrument is repaired, tests should be performed to evaluate the effectiveness of the repair and document that repaired instrument satisfies performance requirements. Agilent offers a service called Repair Qualification (RQ), which refers to the requalification of laboratory instrument hardware after a repair. For some laboratory systems, to document the performance after repair may require a full OQ. However, for some modular or component-based systems, such as HPLC and GC for example, partial qualification testing can be justified. This is accomplished by performing the qualification tests that are applicable to only the module or system component related to the repair, reducing the time the instrument is out of service. Re-qualifying the instrument after repair is a regulatory requirement defined in USP <1058>.

Because of the modular/component-based dependency of RQ service, it is only available for the following instrument platforms: GC, GC/MS, LC, LC/MS, GPC, and SFC.

Agilent offers service contracts to repair and requalify an instrument during the period between scheduled annual OQs.

The level of retesting is prescribed in the RQ section of ACE: a form is displayed for the operator showing all types of repairs possible and the retesting required. Part of an example form for an LC system is shown below.

Re-Qualification After Repair		
Pump Strategies		
Repair/Replace Strategy	Modules	OQ Testing
Internal pump head parts, active inlet valve (or AIV cartridge), (parts of) check valves, reference valves, inlet manifold or pump drive, or taking pump head apart to clean (versus repair)	Any pump	Flow Accuracy & Precision
Pulse damper, pressure transducer	Any pump	Flow Accuracy & Precision
Multi-channel gradient valve	Quaternary	Flow Accuracy & Precision Gradient Composition

The full list of RQ repair and retest guidance is available for customer review.

www.agilent.com/chem/qualification