

<1058> ANALYTICAL INSTRUMENT QUALIFICATION

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INTRODUCTION

■ A large variety of analytical instruments, ranging from a simple apparatus to complex computerized systems, is used in the pharmaceutical industry to acquire data that will help ensure that products meet their specifications. Many of these instruments combine a metrological function with software control. There are many ways of demonstrating that an instrument is qualified and under control, and these can include qualification, calibration, validation, and maintenance. In order to ensure “fitness for purpose”, an integrated approach, based upon a risk assessment, is recommended. For the purposes of this chapter, the term “instrument” includes any apparatus, equipment, instrument, or instrument system used in pharmacopeial analyses.

This informational chapter provides general guidance in a scientific, risk-based approach for carrying out an analytical instrument qualification (AIQ). Detailed instrument operating parameters to be qualified are found in the respective general chapters for specific instrument types. It is left to each laboratory to justify and document its specific approaches. The instrument owners/users and their management are responsible for assuring their instruments are suitably qualified.

This chapter uses various terms, acronyms, and activities common to analytical laboratories and validation disciplines. These terms and activities may not be identical to their usages in all laboratories. The reader is encouraged to be flexible in interpreting the application of these terms and activities in the context and intent of this chapter.

The risk assessment for an AIQ enables the classification of the instrument to determine the extent of qualification and actions needed to demonstrate fitness for purpose. Generally, the more complex the instrument, or the higher the criticality of the measurement, the greater the amount of work that is required to ensure that quality data will be generated. In addition, attention must be paid to ensuring that data integrity and security are maintained.

Instruments can generally be classified as belonging to Groups A, B, or C. It should be noted that the same type of instrument can fit into one or more categories, depending on its intended use.

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. ■ 1S (USP40)

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COMPONENTS OF DATA QUALITY

There are four critical components involved in the generation of reliable and consistent data (quality data). *Figure 1* shows these components as layered activities within a quality triangle. Each layer adds to the overall quality. AIQ forms the base for generating quality data. The other components essential for generating quality data are analytical method validation, system suitability tests, and quality control check samples. These quality components are described below.

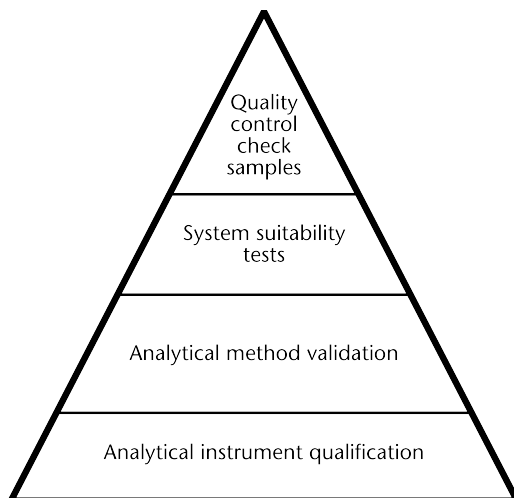


Figure 1. Components of data quality.

Analytical Instrument Qualification

AIQ is the collection of documented evidence that an instrument performs suitably for its intended purpose. Use of a qualified instrument in analyses contributes to confidence in the validity of generated data.

Analytical Method Validation

Analytical method validation is the collection of documented evidence that an analytical procedure is suitable for its intended use. Use of a validated procedure with qualified analytical instruments provides confidence that the procedure will generate test data of acceptable quality. Additional guidance on validation of compendial procedures may be found in *Validation of Compendial Procedures* (1225).

System Suitability Tests

System suitability tests verify that the system will perform in accordance with the criteria set forth in the procedure. These tests are performed along with the sample analyses to ensure that the system's performance is acceptable at the time of the test. *Chromatography* (621) presents a more detailed discussion of system suitability tests related to chromatographic systems.

Quality Control Check Samples

Many analysts carry out their tests on instruments that have been standardized by ¹⁵ (USP40) using reference materials and/or calibration standards. Some analyses also require the inclusion of quality control check samples to provide an in-process or ongoing assurance of the test's suitable performance. In this manner, AIQ and analytical method validation contribute to the quality of analysis before analysts conduct the tests. System suitability tests and quality control checks help ensure the quality of analytical results immediately before or during sample analysis.

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ANALYTICAL INSTRUMENT QUALIFICATION PROCESS

The following sections address the AIQ process in detail. The other three components of building quality into analytical data—analytical method validation, system suitability tests, and quality control check samples—are not within the scope of this chapter.

Qualification Phases

AIQ is not a single, continuous process but instead results from interconnected activities over the lifetime of the instrument. 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 subsequent qualification activities necessary to establish fitness for purpose may be grouped into four phases: design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). PQ is also sometimes called user acceptance testing (UAT). This framework

may be extended for complex systems to include functional specifications (FS) and factory acceptance testing (FAT), if appropriate. Some activities normally undertaken in IQ, OQ, or PQ may be satisfied during the instrument installation and start-up. This is sometimes referred to as site acceptance testing (SAT). It is more important that all required activities be performed in a logical order and scientifically sound manner than the exact allocation within the IQ/OQ/PQ framework. The activities may also be performed as an integrated framework.

Some AIQ activities cover more than one qualification phase, and analysts could potentially perform them during more than one of the phases. However, there is a need for a logical, specific order to the AIQ activities; for example, IQ activities such as configuration must occur before OQ can start. However, where appropriate, qualification activities and associated documentation may be combined together (e.g., IQ and OQ). All AIQ activities should be predefined and contemporaneously documented.

OQ tests are specifically designed to verify the instrument's correct functionality and operation according to specifications in the user's environment, as documented in the URS. Repeating all the testing at regular intervals may not be required. However, following preventative maintenance, critical operational parameters should be confirmed. Routine analytical tests do not constitute OQ testing.

When the instrument undergoes major repairs or modifications, this should be evaluated using change control. Relevant IQ, OQ, and/or PQ tests should be repeated to verify that the instrument continues to operate satisfactorily. If an instrument is moved to another location, an assessment should be made of what, if any, qualification stage should be repeated. ■^{1S} (USP40)

DESIGN QUALIFICATION

■DQ is the documented collection of activities that define the functional and operational specifications and intended purpose of the instrument. DQ states what the laboratory wants the instrument to do and shows that the selected instrument is suitable. DQ may be performed by the instrument manufacturer or the user. 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.

The supplier is generally responsible for robust design and maintaining documentation describing how the analytical instrument and any associated controlling software are manufactured (e.g., design specifications, functional requirements, and others) and tested, sometimes called factory acceptance tests. Nonetheless, the user should ensure that instruments are suitable for their intended application and may evaluate whether the supplier has adopted a quality system that provides for reliable instrumentation, software, and network connectivity. Users should also determine the supplier's capability to support installation, services, and training. This determination might be aided by the user's previous interaction with the supplier.

When use of an instrument changes or it is subject to a major upgrade, it may be necessary to review and/or update the user's DQ documentation. ■^{1S} (USP40)

INSTALLATION QUALIFICATION

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. 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. ■^{1S} (USP40)

Relevant parts of IQ would also apply to a qualified instrument that has been transported to another location or is being reinstalled for other reasons, such as prolonged storage.

The activities and documentation typically associated with IQ are as follows.

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Instrument delivery: Ensure that the instrument, software, manuals, supplies, and any other instrument accessories arrive as specified ■by the user ■^{1S} (USP40) and that they are undamaged. For a pre-owned or existing instrument, manuals and documentation should be obtained.

Description: Document information about the instrument and all components, including supplier(s), model(s), serial number(s), software version(s), and location. ■^{1S} (USP40)

Utilities/Facility/Environment: Verify that the installation site satisfactorily meets ■supplier ■^{1S} (USP40)-specified environmental requirements.

Assembly and installation: Assemble and install the instrument, and perform any preliminary diagnostics and testing. Assembly and installation may be done by the supplier, service agents, specialized engineers, or qualified in-house personnel. Supplier-established installation tests provide a valuable baseline reference for determining instrument acceptance. Any abnormal event observed during assembly and installation merits documenting. IQ documentation packages purchased from a supplier should be reviewed to ensure that they are acceptable to the user before and after execution.

Software installation, network, and data storage: Some analytical systems require the installation of software onto a qualified computer and to be connected to a network for communications and data storage at the installation site. Information technology involvement is often required with computerized laboratory systems. ■^{1S} (USP40)

Installation verification: Perform the initial diagnostics and testing of the instrument after installation. ■When required, connect the instrument to the network, and check its functionality. ■1S (USP40)

OPERATIONAL QUALIFICATION

■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 the contents of the DQ document. Testing activities in the OQ phase may consist of the following test parameters. ■1S (USP40)

Fixed parameters: These tests measure the instrument's non-changing parameters such as length, height, weight, voltage inputs, acceptable pressures, and loads. If the manufacturer-supplied specifications for these parameters satisfy the user, the test requirements may be waived. However, if the user wants to confirm the parameters, testing can be performed at the user's site. Fixed parameters do not change over the life of the instrument, and therefore never need ■to be retested. ■1S (USP40) [NOTE—These tests could also be performed during the IQ phase; ■1S (USP40) if so, fixed parameters need not be retested as part of OQ testing.]

Software functions: Where applicable, OQ testing should include critical elements of the configured application software to show that the whole system works as intended. Functions to test would be those applicable to data capture, analysis of data, and reporting results under actual conditions of use as well as security, access control, and audit trail. The user can apply risk assessment methodologies and can leverage the supplier's software testing to focus the OQ testing effort. ■1S (USP40)

Secure data storage, backup, and archiving: When applicable, test secure data handling, such as storage, backup, audit trails, and archiving at the user's site, according to written procedures.

Instrument function tests: Instrument functions required by the user should be tested to verify that the instrument operates as intended by the manufacturer. ■Supplier ■1S (USP40) information is useful in identifying specifications for these parameters and in designing tests to ■verify that the instrument meets the supplier or user specifications in the user's environment.

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The extent of OQ testing that an instrument undergoes depends on its intended applications, ■therefore no specific OQ tests for any instrument or application are offered in this chapter. Parameters to qualify are described in the general chapters pertaining to a specific analytical technique. ■1S (USP40)

OQ tests can be modular or holistic. Modular testing of individual components of a system may facilitate interchanging of such components without requalification ■but requires a risk assessment to justify it. Holistic tests, which involve the entire system, demonstrate that the whole system complies with user specifications in the DQ.

For OQ test packages purchased from a service provider or supplier, the user must review the material to assure themselves of the scientific soundness of the tests and compliance with applicable regulations. The user should review the documents before execution and approve the tests after execution to ensure completeness and accuracy of the completed document and the test data generated.

Software configuration and/or customization: Any configuration or customization of instrument software should occur before the OQ and be documented. Unless changes are needed for specific component tests, the OQ should be performed using the software configuration that will be used for routine analysis. ■1S (USP40)

PERFORMANCE QUALIFICATION

■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 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.

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.

PQ may include the following activities. ■1S (USP40)

Performance checks: ■A ■1S (USP40) test or series of tests to verify the acceptable performance of the instrument for its intended use. PQ tests are usually based on the instrument's typical on-site applications and may consist of analyzing known components or standards. The tests should be based on good science and reflect the general intended use of the instrument. Some system suitability tests or quality control checks that are performed concurrently with the test samples can be used to demonstrate that the instrument is performing suitably. PQ tests may resemble those performed during OQ, but the specifications for PQ results may be set differently if required. Nevertheless, user specifications for PQ tests should demonstrate trouble-free instrument operation for the intended applications. As is the case with OQ testing, PQ tests may be modular or holistic.

■Testing frequency depends on the ruggedness of the instrument and the criticality of the analytic method. ■1S (USP40) Testing may be unscheduled; for example, each time the instrument is used. It may also be scheduled for regular intervals. Experience with the instrument can influence this decision, ■which should be documented. ■1S (USP40) It may be useful to repeat the same PQ tests each time the instrument is used so that a history of the instrument's performance can be compiled. Alternatively, the instrument may be incorporated into an integrated support system to ensure that it remains continually qualified. ■System suitability tests that are performed concurrently with the test preparations may also ensure that the instrument is performing suitably. ■1S (USP40)

Preventive maintenance and repairs: Periodic preventive maintenance activities are required for many instruments. This may include calibration. Document the preventive maintenance plans, including procedures and frequency as part of the AIQ package. When an instrument fails to meet PQ criteria or otherwise malfunctions, the cause of the failure must be investigated and documented. The instrument may require maintenance or repair. The relevant OQ or PQ test(s) should be repeated after the needed maintenance or repair to ensure that the instrument remains qualified.

Practices for PQ, change control, and periodic review: Each PQ, maintenance, and calibration activity should be documented. Change control should be established to control changes to the instrument configuration, including firmware and software. Critical instruments should have a periodic review to ensure that the system is still under control. Typical areas for review can include qualification/validation status, currency of user procedures, change control records, correctness and completeness of records produced by the system, backup and recovery of electronic records, and review and sign-off of test results.

The instrument owner/user and their management are responsible for this work, although portions can be carried out on his/her behalf by internal staff or external suppliers or service providers. 1S (USP40)

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ROLES AND RESPONSIBILITIES

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. The user's group encompasses analysts, their supervisors, instrument specialists, and organization management. 1S (USP40) Users should be adequately trained in the instrument's use, and their training records should be maintained as required by the regulations.

Users should also be responsible for qualifying their instruments, because their training and expertise in the use of instruments make them the best-qualified group to design the instrument test(s) and specification(s) necessary for a successful AIQ. Consultants, instrument manufacturers or suppliers, validation specialists, and quality assurance personnel can advise and assist as needed, but the final responsibility for qualifying instruments and validating systems lies with the users, who must ensure that the instrument is maintained in a qualified state through routine performance of PQ. 1S (USP40)

Quality Unit

The role of the quality unit in AIQ remains the same as for any other regulated activity. Quality personnel are responsible for ensuring that the AIQ process meets compliance requirements, that processes are being followed, and that the intended use of the instrument is supported by complete, valid, and documented data.

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Manufacturers, Suppliers, Service Agents, and Consultants

Manufacturers are responsible for designing and manufacturing the instrument, and ensuring the quality of relevant processes used in manufacturing and assembly of the instrument. Manufacturers should test the assembled instruments before shipping them to users. To aid the user, suppliers are responsible for developing meaningful specifications for the users to compare with their needs and aid selection.

Where used, software should be developed and tested using a defined life cycle and should have evidence of work performed to support major and minor revisions. Release notes should accompany each version of software released. 1S (USP40)

Finally, it is desirable that suppliers 1S (USP40) should notify all known users about hardware or software 1S (USP40) defects discovered after a product's release; offer user training, service, repair, and installation support; and invite user audits as necessary.

There should be a quality or technical agreement between the user organization and manufacturers, suppliers, service agents, or consultants who supply calibration, maintenance, qualification, or validation services; the agreement should define the scope of work and the responsibilities of the two parties. 1S (USP40)

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SOFTWARE VALIDATION

There is an increasing inability to separate the hardware and software parts of modern analytical instruments. In many instances, the software is needed to qualify the instrument, and the instrument operation is essential when validating the software. Therefore, to avoid overlapping and potential duplication, software validation and instrument qualification can be integrated into a single activity.

Software used for analytical instruments can be classified into four groups: firmware, instrument control software, data acquisition software, and processing software. Although software validation is not the primary focus of this chapter, the following sections describe in which cases this activity is within the scope of the analytical instrument and system qualification.

One source of the validation of software is the guide *GAMP: A Risk-Based Approach to Compliant GxP Computerized Systems*.

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Firmware

Computerized analytical instruments contain integrated chips with low-level software (firmware). Such instruments will not function without properly operating firmware, and in most cases, users generally cannot alter firmware function. Firmware is therefore considered a component of the instrument itself. Indeed, the qualification of hardware is not possible without operating it via its firmware.

Thus, when the hardware (that is, the analytical instrument) is qualified at the user's site, the firmware is also essentially qualified. No separate on-site qualification of the firmware is needed. Whenever possible, the firmware version should be recorded as part of the IQ activities. Any changes made to firmware versions should be tracked through the change control of the instrument (see *Change Control*, below).

In some instruments, firmware can also be capable of fixed calculations on the acquired data. These calculations need to be verified by the user. Some instruments have firmware that enables users to define programs for the instrument's operation; similarly, these user-defined programs need to be defined and verified to demonstrate that they are fit for the intended purpose. Any user-defined programs should be placed under change control and, if possible, access should be restricted to authorized personnel. ■1S (USP40)

Instrument Control, Data Acquisition, and Processing Software

Software for instrument control, data acquisition, and processing for many of today's computerized instruments is loaded on a computer connected to the instrument. Operation of the instrument is then controlled via the software, leaving fewer operating controls on the instrument. Also, the software is needed for data acquisition and post-acquisition calculations. Thus, both hardware and software, their functions inextricably intertwined, are critical to providing analytical results.

The software in this group can be classified into three types: 1) non-configurable software that cannot be modified to change the business process; 2) configurable software that includes tools from the supplier to modify the business process; and 3) configurable software with custom additions (i.e., custom software or macros to automate the business process).

The supplier of the system should develop and test the software according to a defined life cycle and provide users with a summary of the tests that were carried out. Ideally, this software development should be carried out under a quality management system.

At the user site, integrated qualification of the instrument, in conjunction with validation of the software, involves the entire system. This is more efficient than separating instrument qualification from validation of the software. ■1S (USP40)

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CHANGE CONTROL

Changes to qualified instruments, including software, become inevitable as suppliers add new features and correct known defects. However, implementing all such changes may not always benefit users. Users should therefore adopt changes they deem useful or necessary. Changes also occur due to repair, maintenance, or relocation of the instrument. A change control process should be in place to guide the assessment, execution, documentation, and approval of any changes to instrumentation.

Change control applies to all elements of qualification and may follow the general qualification process. Users should assess the effects of changes to determine what, if any, requalification activities are required. If implementation of the change is needed, install the changes to the system. Consider if the change will affect the ability of the instrument to meet the user requirements or if the user requirements have changed. Evaluate which of the existing OQ and PQ tests need revision, deletion, or addition as a result of the installed change.

After implementation, perform any required testing to evaluate the effects of the change. Document all details of the change. Include a description of the change and a rationale, and list appropriate identification (e.g., part and serial numbers of new components and versions of new software or firmware). ■1S (USP40)

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ANALYTICAL INSTRUMENT QUALIFICATION DOCUMENTATION

Documents obtained during qualification activities should be retained in an accessible manner. Where multiple instruments of one kind exist, documents common to all instruments and documents specific to an instrument may be stored

separately. During change control, additional documents may supplement those obtained during the qualification process, and both sets of documents should be retained and maintained in a suitable manner that allows for appropriate protection and access.

Delete the following:

■ INSTRUMENT CATEGORIES

Modern laboratories typically include a suite of instruments and equipment varying from simple nitrogen evaporators to complex automated instruments. Therefore, applying a single set of principles to qualifying such dissimilar instruments would be scientifically inappropriate. Users are most capable of establishing the level of qualification needed for an instrument. On the basis of the level needed, it is convenient to categorize instruments into three groups: A, B, and C, as defined below. Examples of instruments in each group are provided. Note that the list of instruments provided here is for illustration only and is not meant to be exhaustive. It does not provide the exact category for an instrument at a user site. That category should be determined by users for their specific instruments or applications.

The exact grouping of an instrument must be determined by users for their specific requirements. Depending on individual user requirements, the same instrument may appropriately fall into one group for one user and another group for another user. Therefore, a careful selection of groups by users is highly encouraged.

Group A

Group A includes standard equipment with no measurement capability or usual requirement for calibration, where the manufacturer's specification of basic functionality is accepted as user requirements. Conformance of Group A equipment with user requirements may be verified and documented through visual observation of its operation. Examples of equipment in this group are nitrogen evaporators, magnetic stirrers, vortex mixers, and centrifuges.

Group B

Group B includes standard equipment and instruments providing measured values as well as equipment controlling physical parameters (such as temperature, pressure, or flow) that need calibration, where the user requirements are typically the same as the manufacturer's specification of functionality and operational limits. Conformance of Group B instruments or equipment to user requirements is determined according to the standard operating procedures for the instrument or equipment, and documented during IQ and OQ. Examples of instruments in this group are balances, melting point apparatus, light microscopes, pH meters, variable pipets, refractometers, thermometers, titrators, and viscometers. Examples of equipment in this group are muffle furnaces, ovens, refrigerator-freezers, water baths, pumps, and dilutors.

Group C

Group C includes instruments and computerized analytical systems, where user requirements for functionality, operational, and performance limits are specific for the analytical application. Conformance of Group C instruments to user requirements is determined by specific function tests and performance tests. Installing these instruments can be a complicated undertaking and may require the assistance of specialists. A full qualification process, as outlined in this document, should apply to these instruments. Examples of instruments in this group include the following:

- atomic absorption spectrometers
- differential scanning calorimeters
- dissolution apparatus
- electron microscopes
- flame absorption spectrometers
- high-pressure liquid chromatographs
- mass spectrometers
- microplate readers
- thermal gravimetric analyzers
- X-ray fluorescence spectrometers
- X-ray powder diffractometers
- densitometers
- diode-array detectors
- elemental analyzers
- gas chromatographs
- IR spectrometers
- near-IR spectrometers

- Raman spectrometers
- UV/Vis spectrometers
- inductively coupled plasma-emission spectrometers

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Add the following:

■ GLOSSARY

[NOTE—The definitions of these terms may be different than in other *USP* general chapters.]

Calibration: An operation that, under specified conditions, in a first step, establishes a relation between the quantity values, with measurement uncertainties provided by measurement standards, and corresponding indications with associated measurement uncertainties and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication. Note that:

1. A calibration may be expressed by a statement, calibration function, calibration diagram, calibration curve, or calibration table. In some cases, it may consist of an additive or multiplicative correction of the indication with associated measurement uncertainty.
2. Calibration should not be confused with adjustment of a measuring system, often mistakenly called “self-calibration”, or with verification of calibration.
3. Often, the first step alone in the above definition is perceived as being calibration.

Maintenance: Actions performed to keep an analytical instrument in a state of proper function so that it continues to operate within the boundaries set during qualification or validation.

Qualification: Action of proving that any instrument works correctly and delivers the expected results; demonstration of fitness for purpose.

Software configuration: Adaptation of software functions to a business process using tools provided within the application by the supplier of the software.

Software customization: Changing the way software automates a business process by the addition of externally custom-coded software modules using a recognized programming language or the development of macros within the application software.

Software validation: Confirmation by examination and provision of objective evidence that software conforms to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled.

Supplier: This term is used generically and can mean the manufacturer, a vendor, a service agent, or a consultant, depending on the circumstances. ■ 1S (USP40)