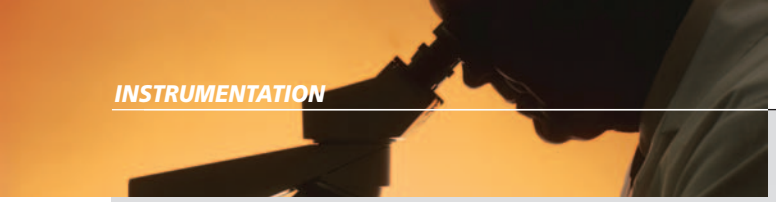

Analytical Instrument Qualification

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In the most general sense, validation refers to a process that consists of at least four distinct components or steps: software, instruments, methods or procedures, and system suitability (1). The system, the software, and the method must all be validated, and system suitability is used to keep the process in check. But while the overall process is called validation, some of the steps also are referred to by that same term, as well as other steps such as qualification and verification.

Before undertaking the task of method validation, it is necessary to invest some time and energy up front to ensure that the analytical system itself is validated, or qualified. Qualification is a subset of the validation process that verifies proper module and system performance before an instrument is placed on-line in a regulated environment. In March 2003, the American Association of Pharmaceutical Scientists (AAPS), the International Pharmaceutical Federation (FIP) and the International Society for Pharmaceutical Engineering (ISPE) cosponsored a workshop entitled "A Scientific Approach to Analytical Instrument Validation" (2). Among other objectives, the various parties (the event drew a cross section of attendees: users, quality assurance specialists, regulatory scientists, consultants, and vendors) agreed that processes are "validated" and instruments are "qualified," finally reserving the term *validation* for processes that include analytical methods–procedures and software development.

The proceedings of the AAPS *et al.* workshop have now become the basis for a new general USP chapter on analytical instrument qualification (AIQ) that is undergoing in-process revision (3, 4). The new chapter ⟨1058⟩ should become official with the first supplement to *USP* 30. The chapter details the AIQ process, data quality, roles and responsibilities, software validation, documentation, and instrument categories. This article will highlight the proposed new chapter; for more information and background the reader is encouraged to review the original documents (2–4).

Components of data quality

The goal of any regulated laboratory is to provide reliable and valid data suitable for its intended purpose. Analysts use validated methods, system suitability tests, and in-process quality control checks to ensure that the data they acquire are reliable and that there are specific guidance and procedures available to ensure compliance (5, 6). Until recently, however, there were no specific guidance or procedures dictating what constituted AIQ, the process of ensuring that an instrument is suitable for its intended application. AIQ is just one component of data quality that also includes software and analytical method validation, system suitability tests, and quality control tests. In general, AIQ and analytical method validation generally ensure the quality of analysis before conducting a test; system suitability and quality control checks ensure the quality of analytical results immediately before or during sample analysis.

While method validation is covered in detail elsewhere (1, 5, 7) and is outside the scope of this article, a brief discussion of system suitability and quality control checks are perhaps necessary. System suitability is the checking of a system to ensure system performance before or during the analysis of unknowns. According to the USP, system suitability tests are an integral part of chromatographic methods (5). These tests are used to verify that the resolution and reproducibility of the system are adequate for the analysis to be performed. System suitability tests are based upon the concept that the equipment, electronics, analytical operations, and samples constitute an integral system that can be evaluated as a whole. Parameters such as plate count, tailing factors, resolution, and reproducibility (%RSD retention time and area for six repetitions) are determined and compared with the specifications set for the method. These parameters are measured during the analysis of a system suitability "sample" that is typically a mixture of main components and expected by-products.

Quality control check samples are run to make sure the instrument has been properly calibrated or standardized. Instrument calibration ensures that the instrument response correlates with the response of the standard or reference material. Quality control check samples also are used often to provide an in-process assurance of the test's performance during use.

The AIQ process

Instruments are qualified according to a stepwise process grouped into four phases: design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ), as outlined in Table I, reproduced here from the *USP* (3). Another way of looking at the AIQ process is sometimes referred to as a time-line approach; as presented in Figure 1, a true chronological order of events takes place.

Design qualification

The AIQ process timeline begins with the DQ phase at the vendor's site, in which the instrument is developed, designed, and produced in a validated environment according to good laboratory practices (GLP), current good manufacturing practices (CGMP), and ISO 9000 standards. Users should ensure that the instrument is fit for their intended use and that the manufacturer has adopted a quality system for development, manufacturing, and testing and has adequate support for installation, service, and training. Vendor-supplied documentation and consumer audits of the vendor are usually sufficient to satisfy users' DQ requirements.

Installation qualification (IQ)

During the IQ phase, all of the activities associated with properly installing the instrument (new, pre-owned, or existing) at the users' site are documented. A system description, including manufacturer, model, serial number, proper site requirements, and the receipt of all of the parts, pieces, manuals, *etc.* necessary to perform the installation is confirmed. During physical installation, all of the fluidic, electrical, and communication connections are made for components in the system. Documentation describing how the instrument was installed, who performed the installation, and other miscellaneous details should be archived. An installation verification confirming the success of the installation also should be performed before proceeding to the next phase.

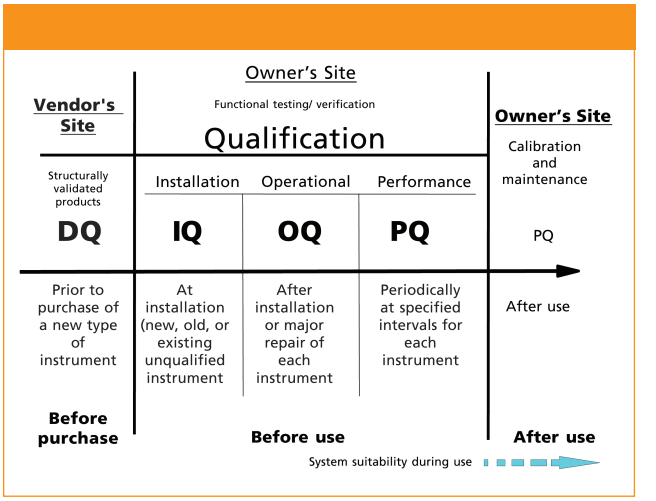

Figure 1: A timeline approach to AIQ.

Operational qualification (OQ)

Once the IQ phase is completed, testing is done to verify that the instrument or instrument modules operate as intended in an OQ phase. First, fixed parameters, for example, length, weight, height, voltage inputs, pressures, and so forth are either verified or measured against vendor supplied specifications. Because these parameters do not change over the lifetime of the instrument, they usually are measured just once. Next, secure data handling is verified. Finally, instrument function tests are undertaken to verify that the instrument or instrument modules meet vendor and user specifications.

Instrument-function tests should measure important instrument parameters according to the instrument's intended use and environment. For liquid chromatography (LC) the following types of tests might be included:

- pump flow rate;
- detector wavelength accuracy;
- gradient linearity;
- injector precision, linearity, and accuracy;
- detector linearity; and
- column oven temperature.

To use an LC detector as an example, an analyst would first verify that the detector performed its startup diagnostic routine. Then, after a suitable warm-up period, wavelength accuracy and linearity tests would be performed. To assess wavelength accuracy, a National Institute of Standards (NIST) traceable standard of erbium perchlorate often is used. Absorbances at three wavelengths (255, 379, and 522 nm) are measured and compared with vendor specifications, taking into account the additive effects of detector and standard variability (as much as 1.5 nm combined). Linearity is assessed by either flushing the cell or filling a cuvette with a known concentration of a standard and calculating response factors at multiple levels (minimum of five). The response factor %RSD is then compared with a predetermined or vendor-supplied specification.

Relevant OQ tests should be repeated whenever the instrument undergoes major repairs or modifications.

Performance qualification (PQ)

Once an IQ and an OQ have been performed, PQ testing is conducted. PQ testing should be performed under the actual running conditions across the anticipated working range. PQ testing should be repeated at regular intervals; the frequency depends on such parameters as the ruggedness of the instrument and the criticality and frequency of use. PQ testing at periodic intervals also can be used to compile an instrument performance history.

In practice, a known method with known, predetermined specifications is used to verify that all of the modules are performing together to achieve their intended purpose. OQ and PQ frequently blend together in a holistic approach, particularly for injector linearity and precision (repeatability) tests, which can be conducted more easily at the system level. For HPLC, the PQ test should use a

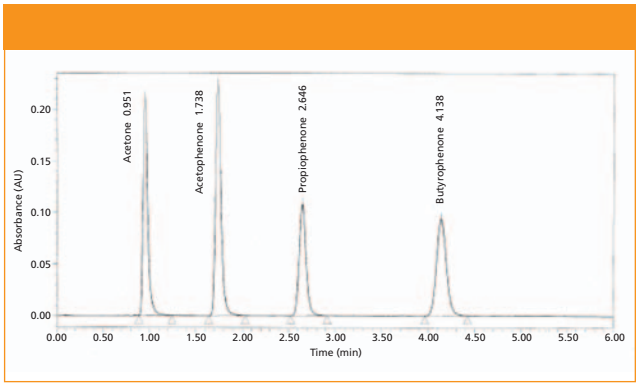

Figure 2: Example of a vendor PQ test. Column: 75 mm × 4.6 mm, 3.5-μm Symmetry C18 (Waters, Milford, Massachusetts); mobile phase: 40:60 (v/v) water–methanol; flow rate: 1.0 mL/min; temperature: 30 °C; detection: UV absorbance at 254 nm; sample: 0.01 mg/mL each analyte in water.

method with a well-characterized analyte mixture, column, and mobile phase. Figure 2 shows an example of a "vendor" PQ test method that incorporates the essence of a holistic OQ and PQ test. Actual user PQ tests should incorporate the essence of the system suitability section of the general chromatography chapter 621 in *USP* (5) to show suitability under conditions of actual use.

Preventative maintenance and repairs

After the instrument is placed on-line in the laboratory, repair (in the case of failure to meet PQ test specifications), and preventative maintenance followed by calibration and standardization are required. Each laboratory should have SOPs in place that define the period of use (usually defined as a reasonable interval during which the instrument operates without any loss in functional performance) and the procedures for placing the instrument on-line following maintenance (OQ, PQ, or system suitability), as well as for proper maintenance and calibration.

Roles and responsibilities

Although consultants, validation specialists, and quality assurance (QA) personnel often will be involved in the AIQ process, the users are the ones that ultimately "own" the process of AIQ and for maintaining the instrument in a qualified state. QA personnel have the responsibility to review the AIQ process to determine that it meets regulatory requirements and to ensure the scientific validity of the process. Manufacturers and developers are responsible for the DQ and for relevant processes used in the manufacturing and assembly of the hardware and software associated with the instrument. Vendors usually make available a summary of these efforts, as well as a test scripts that can be used to qualify the instrument and software at the user's site. Manufacturers also should notify users about hardware or software defects and should offer training, service, and repair.

Software validation and change control

Just about every piece of hardware used in the modern laboratory today is software driven or controlled. Whether it is firmware (integrated chips), software used for instrument control, data acquisition and processing (for example, chromatography data systems), or standalone software such as laboratory information management systems (LIMS), it all must be validated, and resources exist to provide guidance in much more detail than space permits here (8).

Firmware is validated by the manufacturer during DQ, and because it is generally considered to be a part of the instrument itself, when the hardware is qualified, the integrated firmware also is qualified. The same can be said for the chromatography data system; rather than performing a modular validation of the software by itself, the data system is qualified by the user by qualifying the instrument according to the AIQ process in place.

Change control also follows the DQ/IQ/OQ/PQ process as manufacturers add new features and correct known defects in their instrumentation. The change control process enables users to determine which (if any) changes should be adopted, and to assess the effects of changes to determine what, if any, requalification is required.

AIQ documentation

Two types of documents result from AIQ: static and dynamic. Static documents are generated during the DQ, IQ, and OQ phases and should be kept accessible, either electronically or in a separate qualification binder. Static documents can include user manuals, and site requirement documents, for example. Dynamic documents are generated during the OQ and PQ phases, when actual instrument testing takes place. These documents provide a running record for the instrument use and maintenance, and should be kept in a system log book with the instrument and made available for viewing as necessary for anyone interested (that is, the FDA). These documents also should be archived appropriately for future reference and protection.

Instrument categories

Analysts in the regulated laboratory apply a wide range and complexity of instrumentation in their everyday tasks, from balances to mass spectrometers, and the level of complexity dictates the level of qualification. Recognizing the differences, the USP categorized instruments into three groups: A, B, and C.

Conformance of Group A instruments (the lowest level of qualification) to user requirements are determined by visual observation; no independent qualification process is required. Examples of Group A instruments include spatulas, ovens, magnetic stirrers, microscopes, and vortex mixers.

The conformance of Group B instruments to user requirements is determined according to the instruments' SOP, and their failure is usually readily discernible. Examples of instruments that fall into this category are pH meters, balances, thermometers, refrigerators, freezers, and vacuum ovens.

Group C instruments are defined as highly method specific, complex instruments with conformance determined by their application. Full qualification is applied to instruments in this group. Installation of instruments in this group can be quite complicated and is often only undertaken by specialists. Examples include LC and gas chromatography instruments, mass spectrometers, and electron microscopes.

One word of caution regarding the instrument groupings: the exact category that an instrument falls into can be determined only by the user and its intended application.

Conclusion

Data quality is built on the foundation of method and software validation, AIQ, and system suitability. Each of these components plays a critical role in the process of validation. In a regulated laboratory, instruments must generate reliable data, and only a proper AIQ process can fulfill this mission. An approach as outlined in the USP and AAPS committee report that focuses on scientific principles, rather than simply generating paperwork will increase laboratory efficiency and make the validation process less subjective and easier to defend.

Acknowledgments

The author would like to acknowledge Paul St. Jean of Waters Corporation and Ira Krull of Northeastern University for contributions to this manuscript.

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Table I: Timing, applicability, and activities for each phase of AIQ.

DQ	IQ	OQ	PQ
Timing and Applicability			
Prior to purchase of a new instrument	At installment of each instrument (new, old, or existing unqualified)	After installation or major repair of each instrument	Periodically at at specified intervals for each instrument
Activities			
Assurance of vendor's DQ	System description**	Fixed parameters**	Preventive maintenance and repairs
Assurance of adequate support from manufacturer	Instrument delivery		SOPs for operation, calibration, maintenance and change control
Instrument's fitness for use in lab	Utilities/facility/environment		
	Network data and storage	Secure data storage, backup, and archive**	
	Assembly and installation		
	Installation verification**	Instrument function tests**	Performance tests**

**Activities under each phase are usually performed as given in the table. However, in some cases, it may be more appropriate to perform or combine a given activity with another phase. Activities spanning more than one phase are indicated by a double asterisk.