Analytical Instrument Qualification

Standardization on the 4Q Model

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Current GxP regulations require analytical instruments to be qualified to demonstrate suitability for their intended use. Despite the fact that instrument qualification is not a new concept, and even though companies invest a lot of effort in it, related deviations are frequently cited in inspectional observations and warning letters by the US FDA and other regulatory agencies (see "What Inspectors Say," next page).

Many validation professionals working in regulated companies are not sure what exactly to qualify or requalify, test, and document. "How much testing is enough?" they ask. For years, there were no clear standards for equipment qualification like those for analytical method validation. The United States Pharmacopeia (USP) has improved the situation by publishing its chapter <1058> on analytical instrument qualification (**1**). The chapter establishes AIQ as the foundation for data quality and defines its relationships with analytical method validation, system suitability testing, and quality control checks. Similar to analytical method validation, the intent of AIQ is to ensure the quality of each analysis before tests are conducted. By contrast, system suitability and quality control checks ensure the quality of analytical results immediately before or during sample analysis.

Product Focus: Regulated products

Process Focus: Analytical support

Who Should Read: Product and process development, QA/QC, IT

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Level: Intermediate

What the USP Says about AIQ

Two versions of the chapter draft were published in the USP's *Pharmaceutical Forum* in January and August 2005, respectively (**1, 2**). The draft was mainly based on a white paper previously published by the American Association of Pharmaceutical Scientists (AAPS) in 2004 (**3**), which in turn was based on the well-known "4Q" model for equipment qualification (**4**): design, installation, operational, and performance qualification (DQ, IQ, OQ, and PQ, respectively).

Industry forums and suppliers have taken note of the draft publication and are commenting on it and eagerly awaiting a final version. The USP chapter defines certain terminology: *Validation* is used for processes and software; *qualification* is used for instruments. The chapter explains how AIQ fits into other components of data quality: quality control checks, system suitability tests, and analytical methods validation. AIQ serves as the foundation and a prerequisite for those other quality elements. Figure 1 addresses the AIQ process in more detail.

Software and Integrated Systems

For qualification purposes, software is segmented into three categories:

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- Firmware is built into automated instrument hardware (e.g., a controller). This is qualified as part of equipment hardware qualification.
- Manufacturers of instrument control, data acquisition and processing software (e.g., a PC controlling a liquid chromatograph) should validate their software and provide users with a summary of that validation. Software can be qualified by qualifying its related instrument according to the AIQ process.
- Standalone software should be validated during development and tested at user sites.

The USP draft provides specific guidance regarding test methodologies for integrated systems. First, it states that holistic tests are preferred over modular tests for integrated systems. As the term indicates, a holistic test challenges a complete system rather than focusing on a subsystem, module, or subassembly. Correct base functionality is inferred from a successful test of the entire system. Second, USP recommends that instrument firmware (the internal operating system and command

processor of an instrument) does not need to be qualified separately but merely as part of the equipment hardware in the course of such holistic testing. Nevertheless, activities such as firmware upgrades are considered maintenance that must be documented in instrument maintenance records. Instrument suppliers typically deliver system documentation that helps users assess the validation impact of each new firmware release for their instruments.

Computer programs can be validated as a complete system or as stand-alone software. DQ, IQ, OQ, and PQ process activities (and the documented evidence associated with each phase) are subject to change control (Figure 2). Analytical instrumentation is categorized into three groups (A, B, and C), each having different requirements for the extent of qualification (Table 1).

The Four Q Phases

Roles and Responsibilities: The USP chapter clarifies the roles and responsibilities of users, quality assurance units, and equipment manufacturers. Not new, but a critical fact to note is that the ultimate responsibility for instrument operations and data quality resides with end users (analysts, supervisors, operations management), even with the assistance and consultation of validation specialists, QA personnel, and/or suppliers. The QA role has a control and review function for verifying that an AIQ process meets regulatory requirements and that users attest to its scientific validity.

Equipment manufacturers are mostly responsible for DQ during instrument design and validation of their manufacturing, assembly, and software-related processes associated with a given instrument. Their software development must adhere to quality and validation principles. Suppliers can assist users by making available test summaries and scripts (test plans, test cases, test results) and by informing users about system defects reported after release to market. Additionally, these manufacturers should offer training, operational services such as installation, repair and maintenance, and technical support (e.g., phone support, call centers, and on-site support).

Required Documentation: I don't know how often this quote has been repeated, attributed to Ron Tetzlaff and others: "If it is not written down, it didn't happen." The principle is just as true for AIQ activities as for others in a GMP environment. The USP chapter differentiates between "static" and "dynamic" documents (Table 2).

AIQ Instrument Categories: Not all instruments are alike. Analytical laboratories use equipment with a wide range of complexity, ranging from simple tools to very sophisticated analytical devices and automated systems. The USP gives users the responsibility for defining a scientifically sound set of qualification tests for their instruments. Users should be the experts when it comes to instrument functionality, and they need to establish their own qualification requirements based on their intended use of the equipment, on their own knowledge and the results of their own impact analyses.

The USP chapter categorizes instruments into three groups (Table 1). Those three instrument groups are described along with suggested testing coverage but without definition of criteria for assigning a given device to any particular group. Other authors have recently come to similar conclusions (**5**). Group C instruments in particular cover a wide range of complexity, and higher complexity typically increases risk. Unfortunately, the chapter provides little guidance on the operational and maintenance activities that follow deployment. In the scope of USP, AIQ is intended to ensure that instruments are suitable for their intended applications, but it does not account for the fact that many instruments are modules of more complex, computerized systems.

What Inspectors Say

Recent FDA warning letters have cited deviations in the qualification of instrumentation:

"The laboratory does not perform an adequate testing and/or calibration to verify its performance and accuracy."

"The laboratory does not verify that the calibration performed by an outside contractor is complete and performed as required by the established standard operating procedure *HPLC Maintenance and Operational Qualification*. This SOP requires four tests for the operational verification: power up, diagnostics, accuracy, reproducibility and linearity tests. The reproducibility and linearity tests have not been performed."

"During the inspection, the firm did not provide an SOP for the performance verification of the HPLC and GC systems. Actually, they are contracting services for the verification of those systems, and then they are adopting contractor's SOP. Each of them has different SOPs, which includes different types of tests that does not compare [sic]. The firm should establish a procedure to assure uniformity providing specific directions and requirements for all GC Systems. Also, it will apply to HPLC systems.

Comparison with Other Guides

USP uses terminology and applies principles that have been proposed and applied in other relevant guides and guidelines. For example, ICH Q7A provides a similar definition for qualification to that found in the USP chapter: "Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation" (**6**).

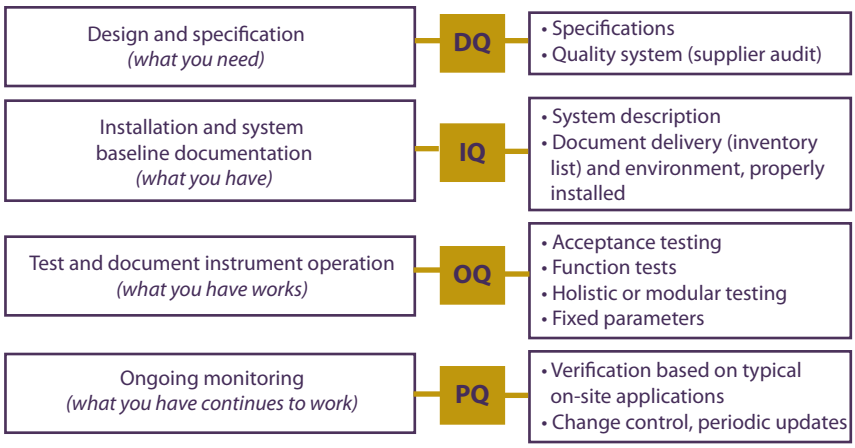
The ISPE's guide to "good automated manufacturing practice" also includes specific definitions and recommendations for validation of computerized systems, including IQ, OQ, and PQ (**7**). The GAMP4 glossary provides the following definitions:

- IQ is "documented verification that a system is installed according to written and preapproved specifications."
- OQ is "documented verification that a system operates according to written and preapproved specifications."

Section 9.15 of the GAMP4 guide states the following:

> IQ confirms that software has been loaded correctly, specified site hardware items have been assembled and installed correctly,

Figure 1: Simplified visualization of the 4Q model



> control and monitoring instrumentation have been calibrated and installed correctly, basic system functions operate on power-up, and any built-in diagnostics are satisfactory. . . .
>
> OQ confirms that operations consisting of hardware and software components will function as specified under normal operating conditions and, where appropriate, under realistic stress conditions, such as alarm and error handling. . . .
>
> Documented verification that the equipment related system or subsystem performs as intended throughout representative or anticipated operating ranges. (7)

Those concepts and definitions sound largely similar, but the USP chapter is limited to commercial off-the-shelf analytical instrumentation and equipment. One author that "this approach is simpler, but the only consideration of the computer aspects is limited to data storage, backup, and archive. Thus, this approach is rather simplistic from the computer-validation perspective" (5).

Recommendations

Develop a standard operating procedure (SOP) for AIQ according to the 4Q qualification model. If you already have one, check to see whether it is in line with the 4Q model. If your SOP proposes a different methodology than 4Q, you need to document your qualification rationale and come up with a scientifically sound rationale explaining how your methodology ensures trustworthy, reliable, and consistent instrument data.

Use one and the same procedure for each instrument category, independent from the vendor and location of a given instrument. Assess which instruments are used for regulated activities and whether data generated by those instruments are subject to a predicate rule. Assess the risk of instrument nonperformance using scientific knowledge.

Define qualification protocols for all the different instrument classes in your laboratory. If necessary and appropriate, work with your instrument suppliers or contract or partner with someone who has a proven track record in the field of instrument qualification services.

Even though it's not covered in the USP draft in very much detail, don't forget the data system. Consider each whole combined system in your integrated validation and qualification approach. Plan additional qualification and acceptance tests to obtain a high degree of assurance that control, communication, and data are accurate and reliable. Look for the final version of the USP chapter and make adjustments, if necessary

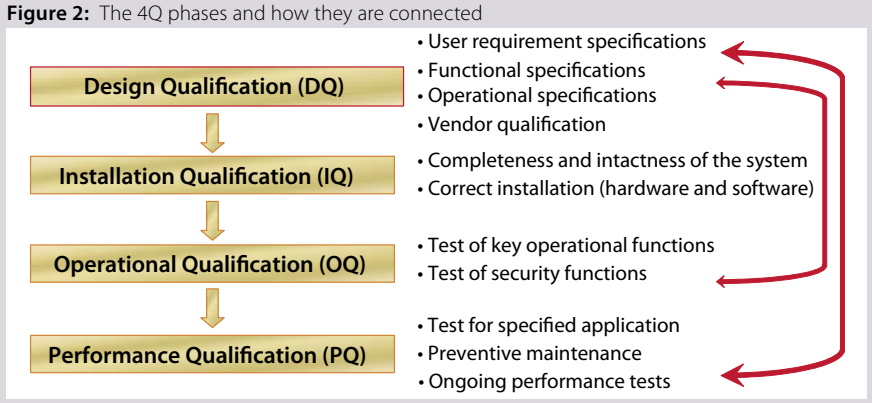
It's All in the Details

World regulatory bodies continue applying science-based and risk-based principles that help us decide where to put the focus in our validation activities. In the context of drug development and manufacture, "risk" always means potential problems for the safety and effectiveness of drug products. The FDA expects regulated companies to also use a risk-based approach when implementing their business processes and practices, especially wherever they relate to regulated activities. USP chapter <1058> is a step forward for the validation community because it establishes the well-proven 4Q-model as the standard for instrument qualification and provides useful definitions of roles, responsibilities, and terminology to steer the qualification-related activities of regulated companies and their suppliers.

4Q helps provide answers to these two critical questions: How can an analytical laboratory prove that a given analysis result is based on trustworthy and reliable instrument data? And how can that laboratory ascertain the validity of its analytical results and show appropriate evidence that each analytical instrument is really doing what the analyst expects it to do — and that the instrument is within the specifications required for a given analysis?

I am convinced that properly maintained and qualified instruments are an important measure for the trustworthiness and reliability of the data they provide. Trustworthy, reliable, and consistent data drive quality-relevant decisions. In a future

Figure 2: The 4Q phases and how they are connected



version of the USP chapter (or in additional chapters), we will be looking for detailed guidance in the area of computerized systems because most complex instrumentation cannot be operated without software (or cannot be used to its full capability without its enabling software).

References

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7 *Good Automated Manufacturing Practice (GAMP) Guide*, Fourth Edition. International Society for Pharmaceutical Engineering: Tampa, FL, 2001.

AIQ Documentation

Static Documents: Documents obtained during DQ, IQ, OQ should be kept in a qualification binder. Those documents common to all instruments should go into one binder or section. And those specific to a given instrument should go into the binder or section specific to it. Under change control, additional documents can be placed with the static ones, but previous documents should not be removed. They can be archived when necessary.

Dynamic Documents: Used during OQ and PQ phases when instruments are maintained or performance tested, these are running records for each instrument. Such "log-books" should be kept with the instruments. Archive as necessary.

Table 1: Instrument categories — not a comprehensive list (categorization can actually vary according to laboratory and/or application).

Category	Qualification Requirements	Examples
A: Simple instruments	Visual inspection Do not require an independent qualification process	Nitrogen evaporators, magnetic stirrers, vortex mixers, mortar and pestle sets, glass pipets
B: Simple instruments for which installation is fairly simple and the causes of failures are readily discernible through simple observations	Qualification (calibration) according to the instrument's standard operating procedures Unambiguous conformity requirements	Balances, incubators, infrared spectrometers, melting-point apparatus, muffle furnaces, light microscopes, pH meters, variable pipettes, refractometers, refrigerator-freezers, thermocouples, thermometers, titrators, ovens, viscosimeters
C: Complex instruments with conformance requirements that are highly specific to method	Conformity bounds are determined by the application Complicated installation may require assistance from specialists Full qualification process	Atomic absorption spectrometers, differential scanning calorimeters, electron microscopes, flame-absorption spectrometers, high-pressure liquid chromatographs, mass spectrometers, microplate readers, thermal gravimetric analyzers, x-ray fluorescence spectrometers, densitometers, diode-array detectors, elemental analyzers, gas chromatographs, near-infrared spectrometers, Raman spectrometers, UV–vis spectrometers, inductively coupled argon-plasma emission spectrometers

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