



by Ron Ball

# Analytical Instruments for Medical Applications Meet the FDA

## Regulations require documented procedures that confirm the validity of instrumentation and data acquisition systems.

Good Manufacturing Practices (GMP) regulations require that companies in the Medical Gas Industry have documented procedures describing how they demonstrate that their test instrumentation and data acquisition components are fit for use. FDA has established this requirement for all analytical instrumentation and data collection components that support any product testing required by 21 CFR, including the USP / NF medical gas monographs. This article discusses the requirements for analysis and data acquisition processes.

A variety of instruments are used in the specialty and medical gas industry to perform analysis and acquire data, to ensure that medical and food gases meet the specifications and requirements established for them. It is also critical that testing verifies that these products do not pose a safety risk from contamination with hazardous substances. An effective analysis of a product should result in obtaining consistent, reliable, and valid data, which would allow someone to decide if a product is safe and suitable for the intended purpose. Depending on the applications, users may need to perform a variety of tasks, which includes validation of their procedures, performance of system suitability tests, conducting in-process quality control checks to document that any data

collected is reliable. With the increasing sophistication and automation of analytical instruments, an escalating pressure is being exerted on users to ensure adequate qualification of their instruments and data collection systems.

### *Ensuring Data Quality*

Four critical components are involved in generating reliable and consistent quality data. These components are shown as layered activities within a quality triangle. (See Figure 1.) Each layer builds off the layer beneath it, and adds to the overall quality and reliability of the process. Ana-

lytical instrument qualification forms the base of the quality triangle. Additional layers essential for generating quality data include analytical method validation, system suitability tests, and quality control checks. Details of each component follow.

—*Analytical Instrument Qualification* consists of documented evidence that offers proof that an instrument and its support systems perform suitably for its designated purpose, that the system is properly maintained and calibrated, and that the analysts are trained and competent. Utilizing a suitably qualified instrument to

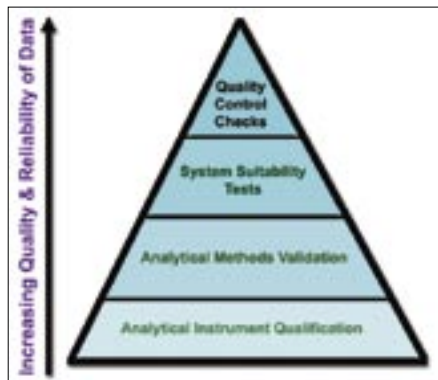
### **Validation versus Qualification**

***Ambiguity exists in the use of the terms “validation” and “qualification”; the terms are often used interchangeably. For the purposes of this article, the term “validation” applies to processes and software, and the term “qualification” applies to instruments. Therefore, the phrase “analytical instrument qualification” (AIQ) refers to the process of demonstrating and documenting that an instrument, in its installed configuration, is suitable for its intended application. The term “validation” is reserved for processes, including analytical procedures and software procedures, and refers to a documented study that demonstrates a high degree of confidence that the process operates as designed, and that no un-intended consequences can result from their operation.***

conduct product analyses ensures confidence in the veracity and reliability of the data generated during testing.

—**Analytical Method Validation** is a documented study that confirms that an analytical instrument (and its support systems) performs in the manner specified; the method can determine and measure all the attributes of the test material required by the procedure. Another use of an analytical method validation is to demonstrate equivalency to a specified method, such as USP/NF medical gas monographs. Use of a validated procedure ensures a high degree of confidence that the procedure will generate test data of acceptable quality.

—**System Suitability Tests** verify that the system will repeatedly perform according to the analyst's expectations, and that it meets the criteria to which it is subject. These tests are included as part of the installed system, and include conducting sample analyses to verify and document the analytical system's acceptable performance.



**Figure 1. Ensuring data quality**

—**Quality Control Checks.** Most analyses are performed on instruments that are calibrated (sometimes referred to as standardized) using reference materials or calibration standards. This process can encompass either a single- or multiple-point calibration, depending on the instrument and its intended application. Calibration of an instrument during analysis ensures that its response correlates with the known properties of the calibration standard or reference material. In addition to periodic calibration, or standardization, some anal-

yses also require the inclusion of quality control check samples to provide an ongoing, in process assurance of the analytical system's suitable performance.

## **Analytical Instrument Qualification (AIQ) Process**

—**Qualification Phases.** Instrument qualification is not a single continuous process; it results from several discrete activities. (See nearby chart.) For convenience, these activities are grouped into four phases: Design Qualification (DQ), Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ). Some of these qualification terms have their roots in manufacturing/process validation; however, the adoption of process validation terms is not meant to imply that all process validation activities are necessary for AIQ. Also, it should be noted that some AIQ activities cover more than one qualification phase and could be performed within any of the phases. While it is important that the required AIQ activi-

ties be performed, it is not as important as during which qualification phase an activity is performed or reported.

### Design Qualification

The instrument developer, or manufacturer, is the party most suited to perform the design qualification (DQ). However, users are responsible for ensuring that instruments are suitable for their intended applications. Also, they must verify that the manufacturer has adopted a quality system for developing, manufacturing, and testing. Users need to verify that manufacturers and vendors adequately support installation, service, and training. Vendor audits or collecting vendor-supplied documentation can satisfy this element of the DQ requirements. The required scope and comprehensiveness of the audits and documentation vary with how familiar the user is with the instrument and his previous interactions with the vendor.

### Installation Qualification

Installation qualification (IQ) is the documentation of activities required to install an instrument in the user's environment. IQ applies to instruments that are new or pre-owned, as well as to any instrument that exists on-site but which has not been previously qualified. Relevant parts of IQ would also apply to a qualified instrument that has been packed and transported to another location. The activities and documentation associated with IQ are as follows:

- **System Description.** Provide a description of the instrument, including its manufacturer, model, serial number, and software version. Drawings and flow charts also should be used where appropriate.
- **Instrument Delivery.** Ensure that the instrument, software, manuals, supplies, and any other accessories arrive with the instrument according to the specifications

in the purchase order, and that they are undamaged. For a pre-owned or existing instrument, manuals and documentation should be obtained.

- **Utilities/Facility/Environment.** Verify that the installation site satisfactorily meets the vendor's specified environmental requirements. A commonsense judgment for the physical environment suffices; one need not measure the exact voltage for a standard-voltage instrument or the exact humidity reading for an instrument that will operate at ambient conditions.
- **Network and Data Storage.** Some analytical systems require network connections and data storage capabilities at the installation site. When required, the instrument should be connected to the network, and its functionality checked.
- **Assembly and Installation.** Assemble and install the instrument, and perform preliminary diagnostics and testing. As-

Qualification Phase Matrix			
DQ	IQ	OQ	PQ
Timing and Applicability			
Prior to purchase	At installation (for new, old or existing unqualified)	After installation or major repair	At periodically specified intervals
Activities			
Assurance of Vendor's design	System Description	Fixed Parameters	Preventive maintenance and repairs
Assurance of adequate	Instrument Delivery		SOPs for operation, calibration, and maintenance
Fitness for use in laboratory	Utilities/Facility/Environment		
	Network and Data	Secure Data	
	Storage	Backup and Archive	
	Assembly and Installation		
	Assembly Verification	Instrument Functions Tests	Performance Checks
<p><b>Note:</b> 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. Performing the activity is far more important than the phase under which the activity is performed.</p>			

sembly and installation of a complex instrument are best conducted by the vendor or specialized engineers; whereas, users can assemble and install simple products. For complex instruments, vendor-established installation tests and guides provide a valuable baseline reference for determining instrument acceptance. Abnormal events observed during assembly and installation merit documenting. If the pre-owned, unqualified instrument or transported instrument requires assembly and installation, the tasks should be performed as specified above, and then the installation verification procedure should be conducted as described below.

- **Installation Verification.** Perform the initial diagnostics and testing of the instrument after installation. Once acceptable results are obtained, the user and (if available) the installing engineer should confirm that the installation was successful before proceeding with the next qualification phase.

### Operational Qualification

After a successful IQ, the instrument should be ready for OQ testing, which includes the following test parameters:

- **Fixed Parameter.** These tests measure the instrument's non-changing parameters (i.e., length, height, weight, voltage inputs, acceptable pressures, and loads). If the vendor-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; therefore, they never need re-qualification.

- **Secure Data Storage, Backup, and Archiving** when required. Test secure data handling, such as storage, backup, and archiving, at the user's site according to written procedures.

- **Instrument Function Tests.** Important instrument functions should be tested to verify that the instrument operates as intended by the manufacturer and required by the user. The user should select important instrument parameters for testing according to the instrument's intended use.

Vendor-supplied information is useful in identifying specifications for these parameters. Tests should be designed to evaluate the identified parameters. Users, or their qualified designees, should perform these tests to verify that the instrument meets vendor and user specifications.

The extent of OQ testing to which an instrument is subjected depends on its intended applications. As a guide to the type of tests possible during OQ, the following, which are applicable to gas chromatographs, should be considered:

- carrier gas flow rate
- detector accuracy and linearity
- column packing
- column oven temperature
- injector precision and accuracy
- peak retention time precision

Routine analytical tests do not constitute OQ testing. The specific purpose of OQ tests is to initially verify that the instrument operates according to specifications in the user's environment. These tests do not need to be repeated at regular intervals. When the instrument undergoes major repairs or modifications, it is recommended that relevant OQ tests be repeated to verify whether or not the instrument continues to operate satisfactorily. Relevant OQ tests should also be repeated when an instrument is transported to another location, although a move within the laboratory, or from one room to another, which does not disturb instrument's operation, may not require re-qualification. It is recommended that firms perform modular testing of individual components of a system whenever possible. This can facilitate interchanging of such components without requiring re-qualification. Having successfully completed OQ testing, the instrument should be qualified to perform sample analyses.

### Performance Qualification

Following the IQ and OQ steps, the instrument's reliability is demonstrated through the performance qualification (PQ). The PQ phase includes the following parameters:

- **Performance Checks.** Set up a series of tests to verify the acceptable perfor-

mance of the instrument for its intended use. PQ tests should be based on the instrument's typical on-site applications. PQ tests are also performed routinely on a working instrument, not only on a new instrument following its installation. User specifications for PQ tests should ensure trouble-free instrument operation for its intended applications. PQ tests are performed independently of the routine analytical testing performed on the instrument. Testing frequency depends on the ruggedness of the instrument and how critical are the tests performed. Testing may be unscheduled; i.e., each time the instrument is used. Alternatively, testing can be scheduled for periodic intervals, such as weekly or monthly; experience with the instrument can influence this decision. Generally, the same PQ tests are repeated each time so that a history of the instrument's performance can be compiled. Some system suitability tests or quality control checks performed concurrently with the test samples also can confirm that the instrument is performing suitably. However, while system suitability tests can supplement periodic PQ tests, they cannot replace them.

- **Preventive Maintenance and Repairs.** When an instrument fails to meet PQ test specifications, maintenance or repair is required. Many instruments require periodic preventive maintenance based on the manufacturer's recommendations. The relevant PQ test(s) should be repeated following maintenance or repair to ensure that the instrument remains qualified.

- **Standard Operating Procedure[s] for Operation, Calibration, and Maintenance.** Establish standard operating procedures to maintain and calibrate the instrument. Every maintenance and calibration activity should be documented, and the documentation maintained according to an established record retention policy.

In deciding the exact approach and the elements necessary for qualifying an analytical instrument and support systems for a particular application and purpose, it is useful to follow a systematic review and decision-making process. It is recom-

mended that firms adopt a risk-based approach, which is a methodology to make and document compliance program decisions. This approach is finding increasing favor with the FDA. With the recent proposed changes to the medical gas monographs by USP, many medical gas firms are adopting new or upgrading existing analytical capabilities. It is important during such a change in capabilities that firms ensure that their processes and systems are validated and qualified in accordance with the requirements of 21 CFR, if the instruments are to be used to analyze medical gases. It is much more cost-effective to consider these requirements at the outset, thereby ensuring adequate information is provided by the instrument manufacturer, and that qualifying and documenting the installed system becomes an integral part of the installation and commissioning process.

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***For more information on FDA regulations and qualifying medical and specialty gas analytical instruments contact Ron Ball at B&R Compliance Associates LLC (317) 297-8518 or visit B&R on the web at [www.brcompliance.com](http://www.brcompliance.com).***