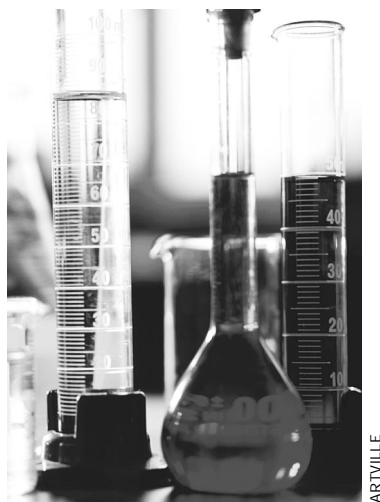


Laboratory Equipment Qualification

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The main goal in qualifying laboratory equipment is to ensure the validity of data. The current equipment qualification programs and procedures used within the pharmaceutical industry are based on regulatory requirements, voluntary standards, vendor practices, and industry practices. The result is considerable variation in the way pharmaceutical companies approach the qualification of laboratory equipment and the way they interpret the often vague requirements. The authors summarize the conclusions of the PhRMA Workshop on Acceptable Analytical Practices for the topic "Qualification of Laboratory Equipment." They describe the areas of agreement and offer options for areas in which there is variation on what is appropriate.

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The concept of Acceptable Analytical Practices (AAPs) was developed by the Analytical Research and Development Steering Committee of the Pharmaceutical Research and Manufacturers of America to share information about how the pharmaceutical industry has implemented the CMC and Quality Guidances of the International Conference on Harmonization and worldwide regulatory authorities. AAPs were designed to provide a process by which one could learn from the experience of experts in pharmaceutical research and development and enhance the understanding of analytical practices that reflect good science and sound regulatory compliance. The process of discussing and publishing AAPs also is intended to identify and address critical issues in which guidance is lacking, ambiguous, or contradictory.

Initially, the process adopted for the development of the first four AAPs involved a two-and-a-half-day workshop held 19–21 September 2000. The four topics discussed were Laboratory Equipment and Instrument Qualification; Out-of-Specification

Results: How to Conduct Laboratory Investigations; Forced Degradation Studies: Issues and Controversies; and Analytical Methods Transfer. This article presents the first of these presentations. The three remaining topics will be covered in future issues of this magazine.

Regulations regarding the qualification of laboratory equipment often are vague and subject to interpretation. The good manufacturing practice requirements state that "the calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met" (1). The good laboratory practice regulations impose similar requirements, stating that "equipment used for the generation, measurement, or assessment of data shall be adequately tested, calibrated, and/or standardized" (2).

Terminology and definitions

In this industry, considerable variation ex-

Equipment qualification definitions

Calibration

The set of operations that establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system, or values represented by material measure and the corresponding values of the measurand (5).

Used by regulatory agencies to refer to the process of checking or adjusting instruments.

Change control

A formal monitoring system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status to determine the need for corrective action that would assure that the system retains its validated state (3).

A formalized program by which qualified representatives review proposed and actual changes to products, processes, equipment, or software to determine their potential effect on the validation status (6).

Started after IQ.

Computerized system

A system that has a computer as a major, integral part. The system is dependent on the computer software to function (7).

Computer hardware components assembled to perform in conjunction with a set of software programs, which are collectively designed to perform a specific function or group of functions (3).

Design qualification

Defines the functional and operational specifications of the instrument and details the conscious decisions of the selection of the supplier (8).

Includes functional requirements and specifications as well as the design specifications.

Equipment

The collective analytical measurement instruments, in conjunction with firmware, assembled to perform a mechanical process.

In a computerized system, the equipment is controlled by the computer system. The computer

collects measurement data from the equipment.

A device or collection of components that perform a process to produce a result (9).

Equipment qualification

The action of proving that any equipment works correctly and actually leads to accurate and reliable results (10).

Includes IQ, calibration, and OQ.

Some include DQ and/or PQ.

Installation qualification

Establishes that the instrument is delivered as designed and specified, that it is properly installed in the selected environment, and that this environment is suitable for the operation and use of the instrument (8).

Documented verification that all key aspects of hardware installation adhere to appropriate codes and the computer system specification (3).

Establishing confidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerances (11).

Instrument

A device (chemical, electrical, hydraulic, magnetic, mechanical, optical, pneumatic) used to test, observe, measure, monitor, alter, generate, record, calibrate, manage, or control physical properties, movements, or other characteristics (12).

A device that takes a physical measurement and displays a value or has no control or analytical function, e.g., stopwatches, timers, and thermometers (9).

Operation qualification

The process of demonstrating that equipment will function according to its operational specifications in the selected environment (8).

Documented verification that the system or subsystem operates as specified in the computerized system specifications throughout representative or anticipated operating ranges (3).

Packaged system

A computerized system in which the computer system and the controlled-function equipment are designed and constructed as an integrated assembly (3).

Performance qualification

The process of demonstrating that an instrument consistently performs according to a specification appropriate for its routine use (8).

Documented verification that the integrated computerized system performs as intended in its normal operating environment, i.e., the computer-related system performs as intended (3).

Process performance qualification

Establishing confidence that the process is effective and reproducible (11).

Process validation

Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (11).

Product performance qualification

Establishing confidence through appropriate testing that the finished product produced by a specified process meets all release requirements for functionality and safety (11).

Requalification and revalidation

Requalification is the repetition of the qualification effort or a selected portion of it (6).

Revalidation is the repetition of the validation effort or a selected portion of it. Requalification is a revalidation activity (6).

Standardization

The assignment of a compositional value to one standard on the basis of another standard (13).

Verification

Confirmation by examination and provision of evidence that specified requirements have been met (14).

ists in the terminology used in the qualification of equipment. The "Equipment qualification definitions" sidebar lists commonly used terms with their definitions. Throughout this document the term *equipment* is used to represent both instruments and equipment as they are defined in the sidebar.

General requirements

The equipment qualification program must be defined and documented. The program must contain provisions for the qualification, maintenance, and documentation of failures of all equipment used to collect data for regulatory submissions. This is usually accomplished by using a standard operating procedure (SOP) that describes the overall program.

Individual procedures, specific to the equipment used, also must be documented. Specific procedures for equipment qualification can be documented in one of two ways: First, separate SOPs can be written that contain the procedures used for qualifying and maintaining each type of equipment. Alternatively, master SOPs can be used to describe the compliance requirements for a variety of

equipment, and specific equipment procedures can be created as separate documents similar to test methods. This second approach minimizes the repetition of the compliance requirements in many SOPs, and it provides additional flexibility in documentation practices.

In addition to the documentation of the program and its associated procedures, all equipment used to generate reportable data must be tagged or labeled and have records maintained. The labeling serves as a way to identify equipment that is unqualified or does not meet performance requirements. It prevents the use of such equipment while it is in its normal operating location. Records usually are maintained through some form of log book that documents all critical activities such as failures, maintenance, qualification testing, location, custodian, and so forth.

Qualification life cycle

It is not necessary to formally document any equipment prepurchase activities. These activities normally are referred to as design qualification, or DQ, and they lead to the selection of equipment. Once the equipment arrives, the installation phase begins. The first part of the qualification cycle requiring formal documentation occurs with the installation qualification (IQ). In addition to specific installation activities, a key part of IQ is to enter the equipment into inventory maintained as part of the program by labeling it and creating the equipment log. In some cases, vendors may require that they perform the installation themselves, resulting in shared documentation of IQ activities.

The qualification life cycle also includes components commonly referred to as operational qualification (OQ) and performance qualification (PQ). Although no requirement exists to separate qualification components into IQ, OQ, and PQ, these terms often facilitate the qualification activities when complex equipment is involved. The OQ testing ensures that the equipment is capable of meeting performance criteria within the ranges used for all of the testing. The selection of OQ tests is based on good science and the intended use of the equipment. The purpose of such tests is to ensure the validity of the data. Suggestions of specific OQ

Examples of operational qualification tests for common analytical equipment

Gas chromatography

Peak retention time precision
Peak area precision
Temperature accuracy of column oven

HPLC

Peak retention time precision
Peak area precision
Accuracy of flow rate
Accuracy of column oven temperature
Detector linearity
UV-vis detector linearity
Gradient accuracy

Capillary electrophoresis

Voltage stability
Peak area precision

UV-vis spectrophotometer

Wavelength accuracy
Photometric accuracy
Wavelength resolution

IR-NIR spectrophotometer

Wavelength accuracy
Wavelength resolution
Photometric accuracy (for quantitative use)

Analytical balance

Calibration

Karl Fischer titrators

Accuracy calibration

Dissolution apparatus

Temperature accuracy
Accuracy of shaft rotation
Equipment performance — USP calibrators
Environmental vibration
Control of paddle centering
Control of distance of shaft to side of vessel

pH meter

Standardization

Polarimeter

Accuracy calibration

tests for various equipment types are listed in the sidebar "Examples of operational qualification tests for common analytical equipment." Depending on the specific use of each type of equipment, the appropriate tests and frequency of testing should be incorporated into the qualification program.

Performance qualification involves the testing of the equipment using the specific method or assay to ensure that the method is producing valid data. PQ may consist of method validation testing, system suitability testing, and analysis and trending of control samples. PQ supplements the OQ by adding checks of the specific method used. Again, like OQ, PQ testing procedures should be based on good science and will depend on the specific method being used.

In summary, the procedures used throughout the entire qualification life cycle must be documented, be based on good science, and ensure the integrity of the data generated by the equipment. The procedures and the functions or components qualified also should be based on the intended use of the equipment. Some qualification should be performed on a periodic basis, and this practice should be defined in the written qualification procedures. The regulations and the supporting science offer no distinction between a manufacturing

quality control laboratory and an R&D laboratory. The same quality standard applies in each situation.

Equipment maintenance

Some OQ testing should be performed following equipment maintenance. The testing should be limited to the operational functions that are affected by the specific maintenance procedure. This usually involves repeating the OQ tests that evaluate the component that has been repaired or replaced. Components that are subject to wear and require routine replacement are best handled with a preventive maintenance program. The preventive maintenance intervals should be defined, be documented, and be an integral part of the qualification life cycle. Intervals can be defined or adjusted on the basis of the actual equipment qualification or maintenance history. Preventive maintenance is performed mainly for business reasons because it represents the most cost-effective method of maintaining equipment that requires frequent service.

Computers and software used to control laboratory equipment

Current regulations require the validation of computers and software that are used to control laboratory equipment or process data. Systems that acquire,

process, or store data also have additional requirements defined by 21 *CFR* 11. Although qualification is considered a subset of validation, validation requires additional documentation and change control procedures. Guidance for validation of computers and software for general computer-related systems and data acquisition systems have been described in Parenteral Drug Association technical reports (3,4). These guidance documents offer procedures for the documentation, qualification, and change control aspects of validation.

When multiple laboratory computers are maintained with the same configuration of hardware and software, complete validation on a single representative unit can be performed. All other identical configurations would require only the IQ portion of the qualification. All such computers must be maintained in the same system of change control, which requires the appropriate revalidation when any change in configuration is made.

Summary and conclusion

The state of equipment qualification practices in the pharmaceutical industry is evolving and is subject to much variation. Although more extensive guidance exists for computerized systems than for non-computerized components of laboratory equipment, the additional validation requirements of the computerized systems present many new challenges. Some commercially available software may not completely meet current requirements.

A need exists for greater consistency in the qualification and maintenance practices for common analytical instruments used within the pharmaceutical industry. In today's environment, there is a tendency to harmonize practices by simply incorporating new procedures into existing programs. In an atmosphere of growing regulatory expectations, this approach is common but not recommended as a means of upgrading qualification programs. The overall program should be evaluated periodically to ensure that current requirements are met and that ex-

cessive or inefficient practices are eliminated or changed. Although variations in equipment qualification practices never can be eliminated within the industry, it is recommended that the industry be consistent in meeting core requirements. This article outlines the core requirements that now are widely accepted. It also offers the rationale for making decisions about topics that are not widely accepted and that will continue to evolve in the industry.

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