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AN OVERVIEW OF ANALYTICAL INSTRUMENT QUALIFICATION WITH REFERENCE OF PHARMACEUTICAL INDUSTRY

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ABSTRACT

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 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. Analytical instruments are used for a specific analysis. So regular performance verifications are made to ensure that the instrument to be used is suitable for its intended application. All equipments used in the production of products shall be properly Validated and Calibrated to demonstrate that it is suitable for its intended purpose. 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 process for instrument qualification follows the 4Qs model approach. It include design qualification (DQ), Installation qualification (IQ), Operational qualification (OQ), Performance qualification (PQ). 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.

Keywords: Qualification, FDA, Instruments, Validation, Calibration, Documentation

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INTRODUCTION

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 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. 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. [1, 2].

Any instrument that is used in the pharmaceutical industries, small laboratories and health care industries is required to always provide reliable and accurate data. Accuracy and integrity of an instrument is established through qualification, calibration and validation. This is very important for all analytical lab instruments, and for everyone in this industry who makes use of such

equipment. Equipment qualification is necessary because it makes these instruments provide data that is valid and is per the requirements of medical device industries. Manufacturers of these instruments normally support their customers in the course of making calibration easy by giving out manuals on how to go about the calibration. [3]

Some useful equipment and instruments that you will find being used in the pharmaceutical industries include:

- Analytical balances
- Melting point apparatus
- Fluorometers
- Active ingredient dissolution test apparatus
- Tablet disintegration test apparatus
- Volumetric titrators
- Leak test apparatus
- PH meters
- Friability test apparatus
- Magnetic stirrer

Components of data quality:

Analytical instrument qualification helps justify the continued use of equipment, but it alone does not ensure the quality of data. Analytical instrument qualification is 1 of the 4 critical components of data quality. Figure 1 shows these components as layered activities within a Quality Triangle. Each layer adds to the overall quality. Analytical Instrument Qualification forms the base for generating quality data. The other essential components for generating quality data are the following: Analytical Methods Validation, System Suit-ability Tests, and Quality Control Checks. These quality components are described below.

Quality control checks
↓
System suitability tests
↓
Analytical method validation
↓
Analytical instrument qualification

Flowchart 1: Components of data quality

Analytical Instrument Qualification (AIQ) is documented evidence that an instrument performs suitably for its in-tended purpose and that it is properly maintained and calibrated. Use of a qualified instrument in analyses contributes to confidence in the veracity of generated data.

Qualification phases: [6]

Qualification of instruments is not a single, continuous process but instead results from many discrete activities. For convenience, these activities have been grouped into 4 phases of qualification.

- ✓ Design Qualification (DQ)
- ✓ Installation Qualification (IQ)
- ✓ Operational Qualification (OQ)
- ✓ Performance Qualification (PQ)

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. Design qualifications are the specifications a manufacturer uses to describe a device or equipment. It seeks to demonstrate that the requirements detailed in the User Requirements Specifications (URS) are all going to be executed satisfactorily before a new design can be authorized. [4] Since the instrument design is already in place for the commercial off-the-shelf (COTS) systems, the user does not need to repeat all aspects of DQ. However, users should ensure that COTS instruments are suitable for their intended applications and that the manufacturer has adopted a quality system for developing, manufacturing, and testing. [5]

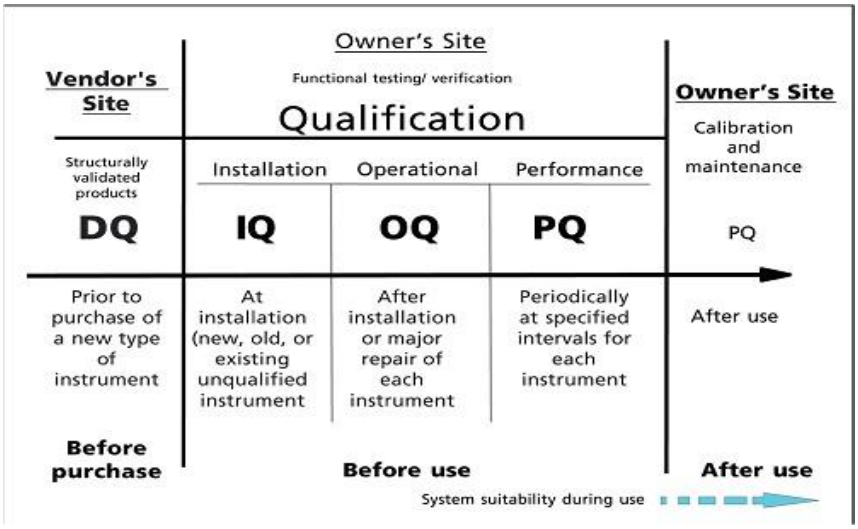

Figure 1: A timeline approach to AIQ

Installation Qualification:

Installation Qualification is a documented collection of activities needed to install an instrument in the user's environment.

- ✓ **System Description:** Provide a description of the instrument, including its manufacturer, model, serial number, software version, etc. Use drawings and flowcharts where appropriate.
  Instrument Delivery: Ensure that the instrument, software, manuals, supplies, and any other accessories arrive with the instrument as the purchase order specifies 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 vendor-specified environmental requirements. A commonsense judgment for the 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 users to provide network connections and data storage capabilities at the installation site. If this is the case, connect the instrument to the net-work and check its functionality.
- ✓ **Assembly and Installation:** Assemble and install the instrument and perform any initial diagnostics and testing. Assembly and installation of a complex instrument are best done by the vendor or specialized engineers, whereas users can assemble and in-stall simple ones. For complex instruments, vendor-established installation tests and guides provide a valuable baseline reference for determining instrument acceptance.
- ✓ **Installation Verification:** Perform the initial diagnostics and testing of the instrument after installation. On obtaining acceptable results, the user and (when present) the installing engineer should con-firm that the installation was successful before proceeding with the next qualification phase.

Operational qualification (OQ):

After a successful IQ the instrument is ready for OQ testing. The OQ phase may consist of these test parameters:

- ✓ **Fixed Parameters:** These tests measure the instrument's non changing, fixed parameters such as length, height, weight, etc. If the vendor-supplied specifications for these parameters satisfy the user, he or she may waive the test requirement. 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 re determining.
- ✓ **Secure Data Storage, Backup, and Archive:** When required, secure data handling, such as storage, backup, and archiving should be tested at the user site according to written procedures.
- ✓ **Instrument Functions Tests:** Test important instrument functions 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 that an instrument undergoes depends on its intended applications. We therefore offer no specific OQ tests for any instrument or application. Nevertheless, as a guide to the type of tests possible during OQ, consider these, which apply to a high-performance liquid chromatography (HPLC) unit:

- pump flow rate
- gradient linearity
- detector wavelength accuracy
- detector linearity
- column oven temperature
- peak area precision
- peak retention time precision

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.

- ✓ **Performance Checks:** Set up a test or series of tests to verify an acceptable performance of the instrument for its intended use. PQ tests are usually based on the instrument's typical on-site applications. Some tests may resemble those performed during OQ, but the specifications for their results can be set differently if required. PQ tests are performed routinely on a working instrument, not just on a new instrument at installation. Therefore, PQ specifications can be slightly less rigorous than OQ specifications. Nevertheless, user specifications for PQ tests should evince trouble free instrument operation vis-à-vis the intended applications.
- ✓ **Preventive Maintenance and Repairs:** When PQ tests fail to meet specifications, the instrument re-quires maintenance or repair. For many instruments a periodic preventive maintenance may also be recommended. Relevant PQ test should be repeated after the needed maintenance or repair to ensure that the instrument remains qualified.
- ✓ **Standard Operating Procedure for Operation, Calibration, and Maintenance:** Establish standard operating procedures to maintain and calibrate the instrument. Use a logbook, binder, or electronic re-cord to document each maintenance and calibration activity.

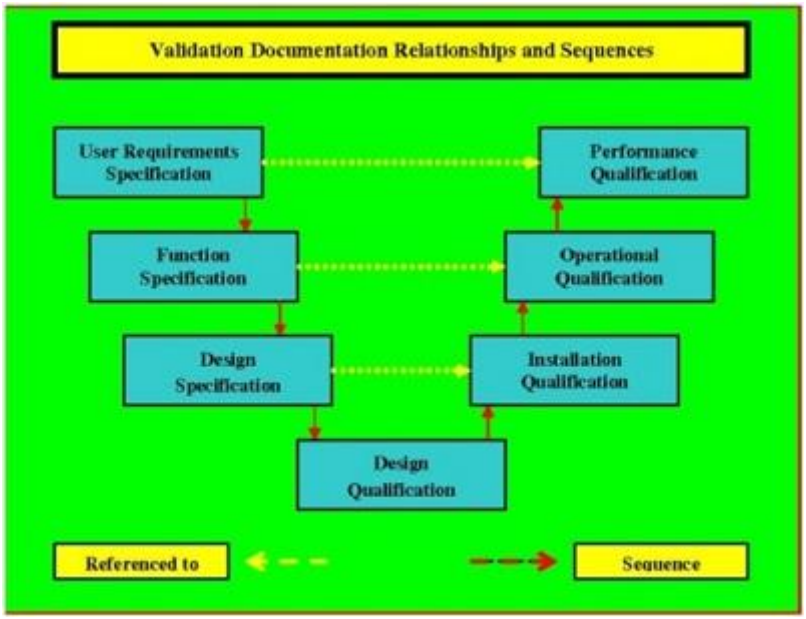

Figure 2: Performance Qualification Relationships

Software validation: Software used for analytical work can be classified into following categories:

- ✓ Firmware
- ✓ Stand-alone software
- ✓ Instrument control, data acquisition, and processing software

Firmware:

The computerized analytical instruments contain integrated chips with low-level software (firmware). Such instruments will not function without properly operating firmware, and users usually cannot alter the firmware's design or function. Firmware is thus considered a component of the instrument itself. Indeed, qualification of the hardware is not possible without operating it via its firmware. So when the hardware; i.e., analytical instrument, is qualified at the user's site, it essentially qualifies the integrated firmware.

Stand-Alone Software:

An authoritative guide for validating stand-alone software, such as LIMS, is available. The validation process is ad-ministered by the software developer, who also specifies the development model appropriate for the software. It takes place in a series of activities planned and executed through various stages of the development cycle. [8]

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

Change Control:

Change Control follows the DQ/IQ/OQ/PQ classification process. For DQ, evaluate the changed parameters, and determine whether the need for the change warrants implementing it. If implementation of the change is needed, install the changes to the system during IQ. Evaluate which of the existing OQ and PQ tests need revision, deletion, or addition as a result of the installed change. Where the change calls for additions, deletions, or revisions to the OQ or PQ tests, follow the procedure outlined below:

- ✓ **Operational Qualification:** Revise OQ tests as necessitated by the change. Perform the revised OQ testing. If the OQ did not need revision, repeat only the relevant tests affected by the change. This procedure ensures the instru-ment's effective operation after the change is in-stalled.
- ✓ **Performance Qualification:** Revise PQ tests as necessitated by the change. Perform the PQ testing after installation of the change if similar testing is not already performed during OQ. In the future, perform the revised PQ testing.

AIQ Documentation:

Two types of documents result from AIQ: Static and Dynamic.

- ✓ **Static Documents**

Static documents are obtained during the DQ, IQ, and OQ phases and should be kept in a "Qualification" binder. Where multiple instruments of one kind exist, common documents should go into one binder or section, and documents specific to an instrument should go into that instrument's binder or section. During Change Control, additional documents can be placed

with the static ones, but previous documents should not be removed.

✓ **Dynamic Documents**

Dynamic documents are generated during the OQ and PQ phase, when the instrument is maintained, or when it is tested for performance. Arranged in a binder or logbook, they provide a running record for the instruments and should be kept with them, available for review by any interested party. These documents may also be archived as necessary.

Instrument Categories:

Modern laboratories typically include a suite of tools. These vary from simple spatulas to complex automated instruments.

✓ **Group A Instruments**

Conformance of Group A instruments to user requirements is determined by visual observation. No independent qualification process is required. Example instruments in this group include light microscopes, magnetic stirrers, mortars and pestles, nitrogen evaporators, ovens, spatulas, and vortex mixers.

Group B Instruments:

Conformance of Group B instruments to user requirements is performed according to the instruments' standard operating procedures. Their conformity assessments are generally unambiguous. Installation of Group B instruments is relatively simple and causes of their failure readily discernable by simple observations. Example instruments in this group include balances, incubators, infrared spectrometers, melting point apparatus, muffle furnaces, pH meters, pipettes, refractometers, refrigerator-freezers, thermocouples, thermometers, titrators, vacuum ovens, and viscometers.

Group C Instruments

Conformance of Group C instruments to user requirements is highly method specific, and the conformity bounds are determined by their application. Examples are as follows:

- Atomic absorption spectrometers
- Differential scanning calorimeters
- Densitometers
- Diode-array detectors
- Electron microscopes
- Elemental analyzers
- Flame absorption spectrometers
- Gas chromatographs
- High-pressure liquid chromatographs
- Inductively coupled argon plasma emission spectrometers
- Mass spectrometers
- Micro-plate readers

CONCLUSION

Data quality is built on the foundation of method and software validation, AIQ, and system suitability. Each of these components plays a significant role in the process of validation. In a regulated laboratory, instruments must produce reliable data, and only a proper AIQ process can fulfill this mission. During all phases of clinical development, including the use of small scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean and suitable for its intended use. Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination. So validation and calibration is very important for analytical instruments

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