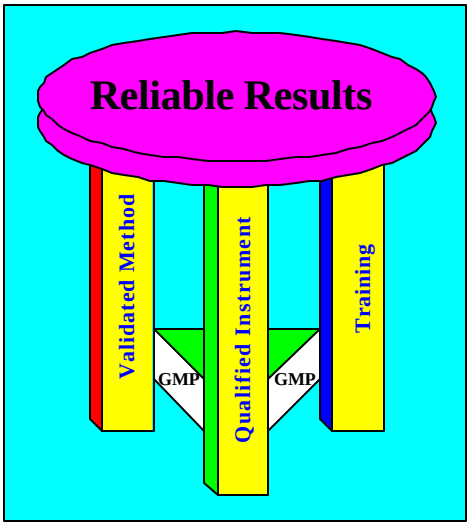
The procurement, qualification and calibration of lab instruments: An Overview

The reliability of analytical data generated from chemical and physical analyses is critically dependent on three factors:



1. Validity of the analytical methods used
2. Reliability of the instruments used for the experiments
3. Proper training of the analysts

These three factors linked together by GMP (Good Manufacturing Practice) provide the fundamental assurance to the quality of the data. In this article, a systematic approach to ensure the reliability of the instruments used in the analyses will be discussed.

Non-reliable instruments can be a major source of error in all analyses. Analytical data generated from instruments which are not properly qualified, nor calibrated with traceable standards are questionable; and hence will be challenged as supportive data in regulatory applications. Regulatory agencies in most countries (eg. Food and Drug Administration (FDA) in the United States; Therapeutic Products Program (TPP) in Canada) demand the use of calibrated instruments for data generation.

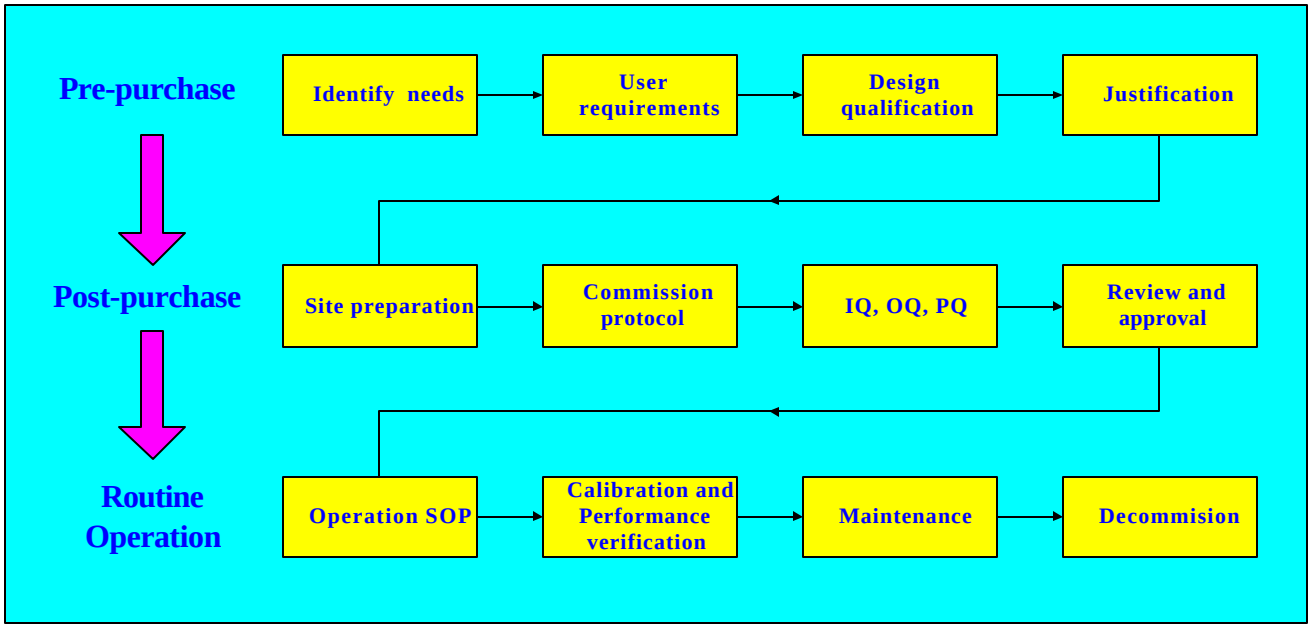
FDA c-GMP requirements (CFR - Code of Federal Regulations, Subpart I: Laboratory Controls, S211.160 (b)(4)):

"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. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used."

The instrument qualification and calibration records are among the most frequently requested items in regulatory inspections. It is vital for the pharmaceutical, biotechnology, environmental, food, cosmetic and chemical laboratories to maintain a vigorous instrument qualification and performance verification program. It is very important to remember that the users are ultimately responsible for the instruments in the laboratory.

A good instrument qualification and performance verification program starts from the decision to bring a piece of new instrument into the laboratory to the decommissioning of the instrument at the end of its useful life. It goes through three phases:

1. Pre-Purchase Phase
2. Post- Purchase Phase
3. Routine Phase



Pre-Purchase Phase

Identify the needs:

The rationale to bring a new piece of instrument into the lab should be well founded. The benefits of acquiring the instrument, such as increasing productivity, meeting a specific need or enhancing the capability of the lab, need to out-weigh the expenditure of valuable and limited resources required to bring the instrument in house and to support its operation.

User requirements:

The users should first decide on the basic functional requirements, which define the type of instrument required to fulfill these needs. For example, a new HPLC system with a variable wavelength UV detector, isocratic pump and an auto-injector is likely to be sufficient for routine

assay of main active ingredient(s) in a pharmaceutical dosage form. However, if the HPLC system is intended to be used for impurities assay, then a system with a gradient pump which provides a wider choice of solvent power for better separation, and a more sensitive detector may be required.

A more detailed system operation requirement can then be defined based on the functional requirement. For example, the flow rate that an isocratic pump has to be able to achieve, the mixing mechanism for a gradient pump, the sensitivity of the detector, the capacity of a variable loop auto-injector etc. All these requirements should be recorded in the user requirement document.

Design Qualification (DQ):

For a custom designed system, the design qualification outlines the key features of the system designed to address the user requirements. For a commercial system, the users usually have very little or no input into the design of the instrument. The design qualification in this case outlines the user requirements and the selection rationale of a particular supplier. Caution should be used when putting together a design qualification since it will have major impact on installation, operation and performance qualifications. The more functions that are specified in the DQ, the more work has to be included in the installation, operation and performance qualification processes.

Justification for acquiring new instruments:

Different emphasis may be used when justifying a new piece of instrument for use in a quality control laboratory as compared to an R&D laboratory. In a quality control environment, the justification is mainly based on the need and also the return on investment. For R&D laboratories, the capability enhancement potential of the new instrument is also a major consideration. The investment in new R&D instruments may not have an immediate return.

There are several other important factors to be considered in the pre-purchase phase:

- Cost - Try to strike a balance between the cost and the performance of the instrument. The least expensive instrument may not be the best investment. The most expensive instrument may not necessary be the appropriate instrument for your operation.

- Ease of use - Simplicity is beauty. The purchasers should think about the general background of the potential users. Not all users are ready to tackle very complicated operations due to time constrains and training.

- Vendor's reliability - The vendor that provides the instrument should have a track record of providing quality instruments and after sale support. A vendor audit should be conducted for a new instrument supplier to evaluate the company's ability to build quality products. Purchasing instrument from a financially unstable vendor is risky.

Since most modern instruments are controlled by computer, it is important to have assurance from the vendor that the software and firmware were developed according to industrial standards such as IEEE software development guide or the Good Automated Manufacturing Practice (GAMP) guide developed by the Parenteral Drug Association. The software development life cycle approach should have been used during the development. Key quality assurance procedures such as change control, security, management involvement and offsite storage should be in place.

- Year 2000 compliance - The operation of the new instrument should not be affected by the transition to the new millenium. As part of the system evaluation process, the user should ask for a written declaration from the vendor before committing to the purchase.

Post-Purchase Phase

Site Preparation:

The users should study the site preparation guide from the vendor. Careful planning is required to ensure the necessary preparations to house the new instrument in the laboratory are completed. Insufficient site preparation causes major inconvenience and long delays in the installation process. It is a waste of time and money to have the engineer show up in the laboratory but not able to do anything due to the lack of site preparation. It is a common mistake to underestimate the effort and time required for site preparation.

The following are the key considerations for the site preparation:

1. Physical dimensions of the instrument and accessories - Make sure there is enough space to accommodate them and the bench is strong enough to support the instrument.
2. Suitable operation environment for the instrument - Proper temperature, humidity and vibration control must be maintained.
3. Utilities - Some instruments will require one or more of the following utilities to operate: custom power supply, electrical plug, gases, computer network connection, special ventilation and enclosure, and water supply. A typical example is the installation of an Inductive Coupled Plasma spectrometer, which requires high electrical current and hence special electrical plug. Installation of LC-MS systems may require the installation of a nitrogen generator. Engineering work to put in these necessary utilities takes time.
4. Health and Safety requirement - eg. Special licenses are required to operate instrument that uses radioactive substances. The CSA (Canadian Standards Association) or UL (Underwriters Laboratory) or Ontario Hydro certification for electrical safety may take time to complete.

Qualification:

Instrument qualification is required to establish the functional capabilities and reliability of the system for its intended use. The instrument qualification can be divided into three stages: Installation, Operation and Performance qualification.

Installation Qualification (IQ): The process to establish that the instrument was received as specified and properly installed in an environment suitable for its operation. Correct installation is the first step to ensure proper functioning of the equipment. Typical IQ activities include:

- Verify hardware and software delivered against shipping list
- Inspect for visible damage
- Verify software and firmware version
- Document the model, configuration and serial numbers of the system components
- Document the model, configuration and serial numbers of the computer system
- Proper power up or boot up of the system components.
- Proper communication between system components and computer control
- All files in the application/control software are downloaded successfully
- Set up instrument logbook
- Calibrate system modules if necessary

Operation Qualification (OQ): The process to establish that the instrument or system modules operate according to specification in a suitable environment. For an HPLC system, the operation of the pump, the injector and the detector will be tested at this stage. Typical OQ tests for the HPLC modules are listed below:

Pump: Flow rate accuracy and gradient accuracy
Detector: Linearity of response, noise, drift, wavelength accuracy
Injector: Precision, linearity and carryover
Column heater: Temperature accuracy

In additional to testing the system components, a functional challenge, which tests the system software operation, should be done. A pre-determined set of instructions can be input step by step into the system. The system responses are then compared to the expected outcomes of the instruction to determine any problems with its execution. Some vendors will provide a standard set of data which can be processed by the system to verify the data handling capability of the system.

Performance Qualification (PQ): The process to demonstrate that the instrument can fulfill the application requirements outlined in the DQ. The PQ can be demonstrated by running a typical application in the DQ which requires the system components to function together properly to deliver the expected test results.

A qualification protocol which provides details about the system, the scope and constraints of the qualification, the qualification tests, test procedures and acceptance criteria should be available for review and approval before the qualification begins. The protocol should also contain an exception log to record any out of specification results, investigation and problem resolution. After the qualification, the test results must be reviewed and approved before the instrument can be put in routine use. The whole qualification process has to be documented. If it is not documented, it is just a rumor!

Involve the users in the qualification process whenever possible. It provides a very good learning opportunity for the users to work with the service engineer during qualification. The users will gain valuable experience with regards to the operation and maintenance of the instrument.

Routine Operation Phase

After the instrument is qualified, the instrument can be used to generate analytical data. A Standard Operating Procedure (SOP) has to be written for the new instrument. The operation instruction, maintenance and calibration should be included in the SOP. It is not necessary to copy the whole operation manual into the SOP. Writing simple instructions with references to the related sections in the manual is a better way. The frequency and the tasks to be performed during maintenance should be stated in the maintenance section. The tests required to calibrate the instrument, the acceptance criteria and the frequency for each test should be included in the calibration section of the SOP.

Definitions of major and minor repairs, which necessitate partial or full system re-qualification, should be included as well. For example, the replacement of a UV lamp in the UV detector does not require a full re-qualification. A replacement of circuitry board will warrant full re-qualification.

Good system maintenance starts with the users. Proper care, which can be as simple as a good system rinsing and clean up after use, can reduce unwanted system failure in the middle of the run and extends the useful life of the instrument. Preventive maintenance is a good investment which will save valuable TIME and MONEY in the long run.

Maintain good usage and service records for the instrument for GMP purposes. The usage records allow the users to be notified in case of system or calibration failure. The user may have to do an impact assessment to determine whether the failure would have affected the reliability of the results generated by the system. The service records will also provide useful information about the system which may simplify the trouble shooting effort in some instances.

The c-GMP requirements dictate that the calibration of instruments should be performed at suitable intervals in accordance with an established written program. Instruments not meeting established specifications shall not be used. Each instrument should have a calibration sticker with information related to the status of the system, when the calibration was performed, who did the calibration and the next calibration date. A systematic program is required to maintain the instruments in a state of calibration. The following points should be considered when setting up an instrument calibration and maintenance program.

- Responsibilities of the personnel involved in the calibration of the equipment
- Frequency of calibration for each type of instrument if it is not covered in the operation SOP of the instrument
- Review and approval of calibration data
- Procedure to issue calibration stickers (database software can be used to track the status of the instrument and help co-ordinate the calibration date)

- Documentation requirements of the calibration and record keeping
- Central filing for instrument related records
- Remedial actions in the event of calibration failure
- Procedure to notify users and obtain impact assessment in case of calibration failure

The terms calibration and performance verification are very often used interchangeably. Calibration involves measuring and adjusting the instrument response using known standards. Performance verification verifies the operation and performance characteristics of an instrument against a pre-determined set of requirements. Calibration is a part of performance verification.

Running system suitability before the analysis cannot replace the need for regular instrument calibration. System suitability only demonstrates the instrument is suitable for a particular application at the time of analysis. It cannot reveal marginal performance of the system. For example, the system suitability test for an HPLC assay using UV detection is not likely to pick up any wavelength accuracy problem since both the standards and the samples are quantitated at the same wavelength. System suitability testing is method specific whereas system calibration verifies the general performance of the instrument.

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