Qualification of High-Performance Liquid Chromatography Systems

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Introduction

Equipment qualification is a formal process that provides documented evidence that an instrument is fit for its intended use and kept in a state of maintenance and calibration consistent with its use (1). The entire qualification process consists of four parts:

- Design qualification (DQ)
- Installation qualification (IQ)
- Operational qualification (OQ)
- Performance qualification (PQ)

General definitions, the overall objectives, and how to select parameters and criteria for of each phase are described in detail in references (1-4). Individual steps and frequency of qualifications depend on the type of equipment and application. This article describes steps required for the qualification of HPLC systems. Qualification steps of other instruments such as UV/Vis Spectrophotometers, Capillary Electrophoresis instruments and Mass-Spectrometers will be described in future articles of this series. This article will focus on qualification of hardware. Qualification of software and computer systems has been described in reference. 5.

To be as practical as possible, a real application scenario from a QA/QC laboratory is used. In case the reader has a different application, the templates can be used as described in this paper, however, the qualification parameters and acceptance criteria should be modified accordingly.

Scenario

A QA/QC laboratory will purchase 15 automated HPLC systems for operation in a Current Good Manufacturing Practice environment. The HPLC systems will be used for compound and impurity analysis. Most of the samples to be analyzed in the laboratory can be run in isocratic mode, but some require gradient analysis. Most of the samples can be monitored with a single wavelength UV signal, but some require in addition peak purity analysis using a spectral UV detector. All instruments should have the same configurations. This has the advantage that they all can be used for all

applications and there is only one test procedure and one set of acceptance criteria required. For instrument control, data acquisition and data evaluation a computer with chromatography software is used.

Design qualification

Design qualification (DQ) describes the user requirements and defines the functional and operational specifications of the instrument. It should ensure that instruments to be purchased have the necessary functions and performance that will enable them be suitable for the intended applications. Later on the DQ document will be used as a basis for tests in the OQ phase.

Table 1 lists elements with examples that should be included in the design qualification for the HPLC systems in the selected QA/QC laboratory. Please note that all instruments are required to have gradient pumps, thermostatted column compartments and diode-array detectors to ensure that they all can be used for all applications.

Design elements	Examples
Intended use	Analysis of drug compounds and impurities
User requirement specification for the HPLC analysis	• Up to 100 samples / day • Automated over-night analysis • Limit of quantitation: 0.1% • Automated confirmation of peak identity and purity with diode-array detection • Automated compound quantitation and printing of report
Functional specifications	
Pump	Binary or higher gradient
Detector	UV/Vis Diode-array, 190-900 nm
Autosampler	100 samples, 0.5 ul to 5 ml sample volume
Column compartment	15 to 60 Deg C, peltier controlled
Computer	System control, data acquisition for signals and spectra, peak integration and quantitation, spectral evaluation for peak purity and compound confirmation. Electronically save all chromatograms generated by the system.
Operational specifications	Detector: Baseline noise: <5 x 10-5 AU • Sampler: Precision inj. volume: <0.5% RSD, sample carry over: <0.5% • Pump: precision of retent.time: <0.5% RSD
User instructions	• Operational manual on paper • Computer based tutorial
Validation/qualification	Vendor must provide procedures and services for IQ and OQ
Maintenance	• Vendor must deliver maintenance procedure and recommend schedule • Instrument must include early maintenance feedback for timely exchange of most important maintenance parts • Maintenance procedures must be supplied on Multimedia CD ROM
Training	Vendor must provide familiarization and training

Table 1. Design qualification elements.

Installation qualification

Installation qualification establishes that the instrument is received 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. Table 2 lists steps as recommended before and during installation. IQ should include analysis of a test sample. A successful run of such a sample verifies correct installation of all modules and electrical and fluid connections.

Before installation

- Obtain manufacturer's recommendations for installation site requirements.
- Check the site for the fulfillment of the manufacturer's recommendations (utilities such as electricity, and environmental conditions such as humidity and temperature).
- Allow sufficient shelf space for the equipment, SOPs, operating manuals and software.

During installation

- Compare equipment, as received, with purchase order (including software, accessories, spare parts)
- Check documentation for completeness (operating manuals, maintenance instructions, standard operating procedures for testing, safety and validation certificates)
- Check equipment for any damage
- Install hardware (computer, equipment, fittings and tubings for fluid connections, columns in HPLC and GC, power cables, data flow and instrument control cables)
- Switch on the instruments and ensure that all modules power up and perform an electronic self-test
- Identify and make a list with a description of all hardware, include drawings where appropriate.
- Run test sample and compare chromatogram print-out with reference chromatogram
- List equipment manuals and SOPs
- Prepare an installation report

Table 2. IQ steps before and during installation (from reference 2)

Operational qualification (OQ)

Operational qualification (OQ) is the process of demonstrating that an instrument will function according to its operational specification in the selected environment“ It verifies that the HPLC system complies with key functional and operational requirements as specified in the design qualification.

In modular HPLC systems it is recommended to perform system tests (holistic testing), rather than performing tests module by module (modular testing). Individual module tests should be performed as part of the diagnosis if the system fails. Furman and Layloff, two US FDA employees (6) have first promoted this holistic approach computerized HPLC systems.

Table 3 includes test parameters, procedures and recommended user limits. At the beginning of the test, a leak test based on the instrument's flow rate accuracy is performed. If this test fails, most other tests are likely to fail. Reference 3 gives further background information on the selection of parameters and acceptance limits.

Parameter	Procedure (*)	User Limit
Leak testing	Flow test by volume or weight/time	± 5 %
Baseline drift	ASTM Method E19.09, 20 min	<2 x 10-3 AU
Baseline noise	ASTM Method E19.09, 20 x 1 min	<5 x 10-5 AU
Precision of injection volume	6 x injection of caffeine standard, RSD of peak areas	0.3 % RSD
Precision of flow rate	6 x injection of caffeine standard, RSD of retention times	0.5 % RSD
Detector linearity	inject 5 standards	>1.5 AU, 5%
Wavelength accuracy	holmium oxide filter	± 1 nm
Temperature accuracy	comparison with external measuring device	± 1 °C
Temperature precision	monitoring temperature over 20 min	± 0.25 °C
Autosampler carry over	Injection of blank solvent after large concentration	< 0.5 %
Mobile phase composition accuracy	Step gradients from 4 to 7 % B, step heights relative to 100%, with acetone tracer	± 1 %

(*) For detailed procedure, see reference 7

Table 2. Test parameters and acceptance criteria for case study.

Performance qualification

Performance Qualification (PQ) is the process of demonstrating that an instrument consistently performs according to a specification appropriate for its routine use. Important here is the word 'consistently'. The test frequency is much higher than for OQ. Another difference is that PQ should always be performed under conditions that are similar to routine sample analysis. For a chromatograph this means using the same column, the same analysis conditions and the same or similar test compounds.

PQ should be performed on a daily basis or whenever the instrument is used. The test frequency not only depends on the stability of the equipment but on everything in the system that may contribute to the analysis results. For a liquid chromatograph, this may be the chromatographic column or a detector's lamp. The test criteria and frequency should be determined during the development and validation of the analytical method.

In practice, PQ can mean system suitability testing, where critical key system performance characteristics are measured and compared with documented, preset limits. For example, a well-characterized standard can be injected 5 or 6 times and the standard deviation of amounts are then compared with a predefined value. PQ tests are applications specific. If the limits of detection and/or quantitation are critical, the lamp's intensity profile or the baseline noise should be tested. They should use the same column and chemicals as used for the real samples. Test should include

- precision of the amounts
- precision of retention times
- resolution between two peaks
- peak width at half height or
- peak tailing
- baseline noise
- wavelength accuracy of the UV/Visible wavelength detector, preferably using built-in holmium-oxide filters

Documentation

On completion of equipment qualification, documentation should be available that consists of:

- Design qualification document
- IQ document (includes description of hardware and software)
- Procedures for OQ testing
- OQ test reports
- PQ test procedures and representative results

OQ test reports should include test parameters, acceptance criteria and actual results. An example of a typical test report is shown in figure 1.

Test method:	C\HPCHEM\1\VERIF\Check.M		
Data File Directory:	C\HPCHEM\1\VERIF\Result.D		
Original Operator	Dr. Watson		
Test item	**User limit**	**Actual**	**Com**
DAD noise	<5x10-5AU	1x10-5AU	Pass
Baseline drift	<2x10-3AU/hr	1.5x10-4AU/hr	Pass
DAD WL calibration	±1 nm	±1 nm	Pass
DAD linearity	|1.5 AU	2.2 AU	Pass
Preci. of ret.times	<0.3 % RSD RT	0.15 % RSD RT	Pass
Temp.stability	±0.15 °C	±0.15 °C	Pass
Precision of peak area	< 0.5% RSD	0.09 % RSD	Pass
Verification Test Overall Results		Pass	
HP 1100 Series System, Friday, January 16, 1998			
Test Engineer			
Name:		Signature:	

Figure 1. OQ report obtained from the HP ChemStation for the HP1100 Series HPLC (from ref 2)

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