Chapter 3

Qualification of Analytical Instruments

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Qualification of Analytical Instruments

Equipment qualification and validation of computerized systems cover the entire life of a product. It starts when somebody has a need for a specific product and ends when the equipment is retired. For computer systems validation ends when all records on the computer system have been migrated and validated for accuracy and completeness on a new one. Because of the length of time and complexity the process has been broken down into shorter phases, so called lifecycle phases. Several lifecycle models have been described for qualification and validation. Most common ones are the V and 4Q model. The V model includes code development and code testing for software, which is important when validation also covers software development. For the purpose of this primer, where we deal with commercially available instruments and systems, we have selected the 4Q model with phases such as design qualification (DQ), installation qualification (IQ), operational qualification (OQ), performance qualification (PQ). The process is illustrated in figure 2.

Good to know!

All activities are defined in a validation or qualification plan and results are documented in a summary report.

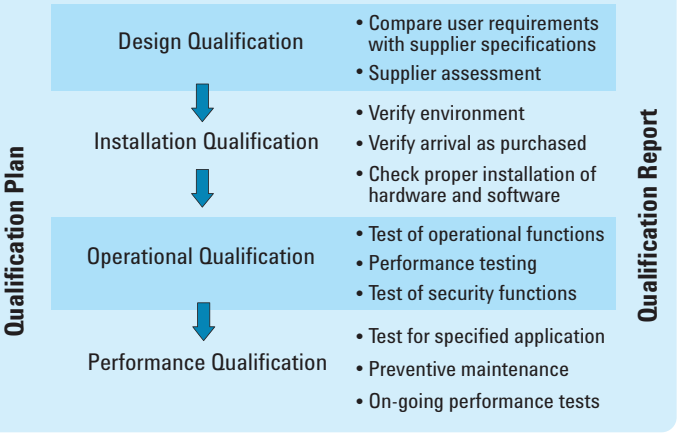

Figure 2
Qualification phases – 4Q model.

In the DQ phase user requirements are compared with the vendor's specification. In addition, users conduct an assessment of the vendor. In the installation qualification the selected user's environment is checked whether it meets the vendor's environmental specifications. The instrument

is installed according to vendor's recommendations and correct installation is verified and documented. Operational qualification checks if the instrument conforms to the functional specifications, as defined in the DQ phase. Performance qualification verifies that the complete system works for selected applications. Preventive maintenance activities and controlled changes also are part of this phase. All activities are defined in a validation or qualification plan and results are documented in a summary report. Figure 3 illustrates the timeline for the four qualifications.

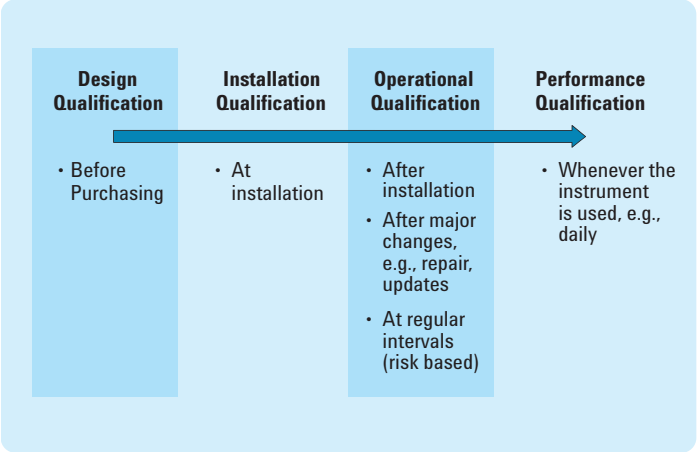

Figure 3
Qualification time line.

3.1 Qualification Planning

Qualification activities should be described in a master plan. The plan documents a company's approach for specific activities, for example, how to qualify analytical instruments, how to assess vendors or what to test for commercial computer systems. A master plan serves two purposes: when implemented right, it ensures consistent and efficient implementation of equipment qualifications, and it answers an inspector's question for a company's approach for instrument qualification and system validation. A validation master plan is also officially required by Annex 15[22] to the

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European GMP directive: "All validation activities should be planned. The key elements of a validation program should be clearly defined and documented in a Validation Master Plan (VMP) or equivalent documents". FDA regulations and guidelines do not specifically require a validation master plan. However, inspectors want to know what the company's approach towards validation is. The qualification master plan is an ideal tool to communicate this approach both internally and to inspectors. In case there are any questions as to why things have been done or not done, the master plan should provide the answers.

Good to know!

A validation master plan is officially required by Annex 15 to the European GMP directive.

Within an organization a validation master plan can be developed for:

- the entire company at a corporate level
- multiple or single sites
- departments
- system categories

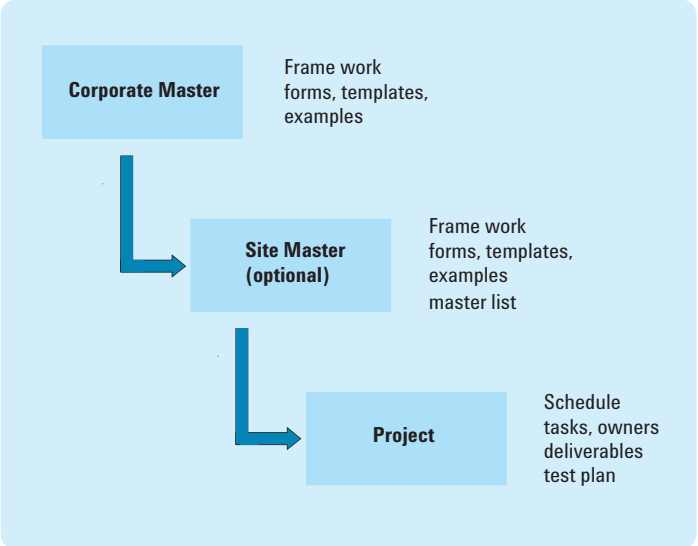
The master plan is a framework for individual project plans and should be written at the highest level possible. This ensures consistent implementation across an organization.

Equipment and computer validation master plans should include:

1. Introduction with a scope of the plan, e.g., sites, systems, processes
2. Responsibilities, e.g., user departments, QA, IT
3. Related documents, e.g., risk master plan
4. Products/processes to be validated and/or qualified
5. Qualification/validation approach
6. Risk assessment
7. Steps for equipment qualification and computer system validation with examples on type and extent of testing
8. Vendor assessment
9. Handling existing systems
10. Change Control procedures and templates
11. Instrument obsolescence and removal
12. Training plans (system operation, GMP)
13. Templates and references to SOPs
14. Glossary

For each individual project a validation project plan should be developed. This plan is derived from the validation master plan.

Figure 4 shows the link between the master plan and project plan. Ideally master plans are developed at a corporate level. Project plans are written in departments specifically for an instrument or system. Depending on the size, structure and geographic distribution there also may be a site or country specific master plan that is derived from the corporate master plan but has been customized according to specific circumstances and requirements of that site.



Figue 4
Link between master plan and project plan.

The project plan outlines what is to be done in order to get a specific system into compliance. For inspectors it is a first indication of the control a laboratory has over a specific instrument or system and it also gives a first impression of the qualification quality.

For simple equipment qualification a template in table form can be used to outline planned activities. A template example is shown in Figure 5. The left column can be the same for all instruments in the same category, which makes the whole qualification process very efficient.

Scope of the Plan	
Product Description	
Validation Strategy	
Responsibilities	
Supplier Assessment	
Risk Assessment	
Testing Strategies	
DQ	
IQ	
OQ	
PQ	
Traceability Matrix	
Procedures	
Documentation Control	
Approval	

Figure 5
Template for instrument qualification project plan.

3.2 Design Qualification

"**D**esign qualification (DQ) is the documented collection of activities that define the functional and operational specifications of the instrument and criteria for selection of the vendor, based on the intended purpose of the instrument"[2].

Design qualification is a shared responsibility between the vendor and the user of an instrument.

The vendor's responsibilities are to:

- Design, develop and manufacture instruments in a quality control environment.
- Develop functional and operational product specifications.
- Provide information on how software and instruments are validated. during development and supported during the entire life of the products.
- Allow user audits, if required, and share approaches for development and testing.

The user's responsibilities are to:

- Describe the analysis problem and selection of the technique.
- Describe the intended use of the equipment.
- Describe the intended environment (including computer environment).
- Select and document the functional and performance specifications (technical, environmental, safety).
- Select and assess the vendor.

Specifications

DQ should ensure that instruments have all the necessary functions and performance criteria that will enable them to be successfully implemented for the intended application and to meet business requirements. Errors in DQ can have a tremendous technical and business impact, and therefore a sufficient amount of time and resources should be invested in the DQ phase. For example, setting wrong operational specifications for an HPLC system can substantially increase the workload for OQ testing, and selecting a vendor with insufficient support capability can decrease instrument up-time with a negative business impact.

Figure 6 shows a template that can be used to document design qualification. User requirements for an HPLC system should not only have a section to define chromatographic functions and performance but also for physical requirements, construction and vendor requirements to the vendor. A physical requirement could be that all modules should have the same dimensions to allow stackability for optimal use of the lab's bench

Function/ Performance	User Requirements	Supplier Specification	Pass/Fail
Function 1			
Function 2			
Physical Requirements			
Construction Requirements			
Vendor Requirements			

Figure 6
Template for design qualification.

space. An example of a construction requirement are accessibility of the detector lamp and flow cell from the front of the instrument for easy maintenance.

Figure 7 shows an example of selected functional and performance specifications of an HPLC system. The user defines his/her requirement specifications and compares them with the vendor's specifications. To set the functional and performance specifications, the vendor's specification sheets can be used as guidelines. However, it is not recommended to simply copy the vendor's specifications, because compliance to the functional and performance specifications must be verified later in the process during operational qualification and also when re-qualifying the instrument at a later time. Specifying too many functions and setting the values too stringently will significantly increase the workload for OQ. For example, if a company has a need for an isocratic HPLC system, but plans to purchase a gradient system for future use, only an isocratic system should be formally specified for regulatory purposes. This means, as long as the instrument is not used for gradient runs no gradient test need to be conducted. Later on, when the system is used for gradient analysis, the specifications should be changed through a change control procedure.

The specifications should be set so that there is a high likelihood that the instrument conforms to them, not only during initial OQ but also during requalification, for example, a year later. Otherwise users may be expected

Function/ Performance	User Requirement	Vendor Specification	Pass/Fail
Autosampler capacity	>90 x 2 mL vials	100 x 2 mL vials	passed
Injection volume precision	<1 % with 10 µL injection volume	<0.5 % with 10 µL injection volume	passed
Flow rate range	1-5 mL/min	0.1-10 mL/min	passed
Baseline noise	$<\pm 2 \times 10^{-5}$ AU	$<\pm 4 \times 10^{-6}$	passed
Keyboard control	Control through local user interface	Control through local user interface	passed

Figure 7
Selected HPLC specifications for design qualification.

to initiate an investigation to determine if the non-qualified instrument could have had a negative impact on the quality of the product. For example, these possibilities are expressed in ICH Q7A[19]:
"Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration".

Good to know!

Vendors of critical analytical instruments should be qualified through a formal process.

Vendor Assessment

Vendors of analytical instruments should be qualified through a formal process. The objective is to ensure that vendors provide high quality products and can give adequate support. For basic equipment, such as pH-meters or a balance, this can be a single page statement describing why the vendor XY has been selected. Certification for a recognized quality system is sufficient for simple instruments. The formal assessment statement should be supported by the quality systems certificate. Figure 8 shows a template with examples to document vendor assessment criteria for analytical instruments.

Requirements	Results	Passed
A Leader in the Market Place		☐ yes ☐ no
Good Experience with the Vendor		☐ yes ☐ no
Quality Assurance		
ISO Certification		☐ yes ☐ no
Documented Software Development		☐ yes ☐ no
Support		
Provide Specifications List		☐ yes ☐ no
Installation Service		☐ yes ☐ no
IQ/OQ Services		☐ yes ☐ no
Phone and Onsite Support		☐ yes ☐ no

Figure 8
Selected criteria for vendor assessment.

For more complex systems especially for critical computer systems such as chromatographic data systems a more detailed assessment is recommended. Depending on the complexity and criticality of the system this can be a mail audit, 3rd party audit and a direct audit through the user firm.

The purpose of the vendor assessment is to ensure that products are designed, developed and manufactured in a documented quality environment. The assessment should also verify that the vendor provides the right services and can maintain the instrument through phone and on-site support.

3.3 Installation Qualification

"Installation qualification (IQ) is the documented collection of activities necessary to establish that an instrument is delivered as designed and specified, is properly installed in the selected environment, and that this environment is suitable for the instrument"[2].

Good to know!

Responsibility for IQ lies with the user but activities should be supported and can be carried out by the vendor.

Responsibility for IQ lies with the user but activities should be supported and can be carried out by the vendor. For example, before the instrument arrives, the vendor should provide the user with environmental specifications so that the user can prepare the installation site accordingly.

Tasks performed for IQ include:

- Prepare the laboratory facility according to vendor environmental specifications.
- Control and record environmental conditions, if critical. For example, temperature and humidity.
- Compare equipment received with the purchase order (including, accessories and spare parts).
- Check equipment for any damage.

Good to know!

Agilent Technologies provides documentation and services for installation qualification.

- Verify that the instrument conforms with physical and construction requirements, as specified by the user.
- Check documentation for completeness (operating manuals, maintenance instructions, standard operating procedures for testing, safety and validation certificates).
- Install hardware (instrument, fittings and tubing 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.
- List equipment manuals and SOPs.
- Record firmware revision.
- Prepare an installation report.
- Enter instrument data into an inventory data base.
- Prepare, review and sign formal IQ documentation.

Figure 9 shows a template with selected examples that can be used to document completeness of shipment. Figure 10 shows an example of how to check if construction requirements such as stackability and accessibility of flow cells are met.

Purchase Order Item	Complete yes/no, Comment
UV Detector	
10 µL Flow Cell	

Manual Item	Complete yes/no, Comment
Operating Manual	yes
Lamp	yes
Power Cord	yes
LAN Cable	yes
2 x Tubings with Fittings	yes

Figure 9
Template and examples to document completeness of shipment for IQ.

Requirement	Expected Result	Pass/Fail
Accessibility of flow cell and lamp from front	Flow cell and lamp must be accessible from front	Pass
Detector must be stackable with other 1200 Series HPLC modules	All modules have the same width and depth	Pass

Figure 10
Verification of construction requirements for IQ.

All instruments should be entered into the IQ protocol and/or into a database. An example of this documentation is shown in figure 11. The IQ documents should be updated whenever there is a change made to any entry in the IQ documents. Examples of changes are a firmware revision and the location of the instrument within a building or site.

Identification	
Manufacturer	Best HPLC
Model	D4424A
Firmware revision	1.00
Serial Number	E4431A
Internal ID (Asset number)	D33243
Current location	Glab4
Size (w x b x h) (cm)	30 x 22 x 7
Condition when installed	New
Supplier contact phone for services	1+541-64532

Figure 11
Equipment documentation for IQ.

Testing for Installation Qualification

Installation should verify that the instrument hardware and software are properly installed. It does not verify that the instrument conforms to the functional and performance specification. This is done later in the OQ phase. For individual modules, testing is limited to perform and document the instruments self diagnostics when it is switched on.

For systems comprised of multiple modules, correct connection between the modules should be verified. For a modular analytical system, this can be easily achieved by running a test sample and comparing the output with a reference plot. An example of test specifications and results are shown in figure 12.

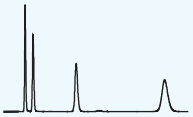
Actions	Expected Result	Pass/Fail
1) Set instrument conditions according to the installation manual for analyzing the installation verification sample	A chromatogram similar as in the installation manual is obtained. 	
2) Inject the installation verification sample	1. Chromatogram must include four peaks.	1) pass
	2. First two peaks are higher than the last two a peaks	2) pass
	3. Retention time of 3rd peak should be between 2.5 and 3.5 minutes	3) pass

Figure 12
Verification of correct system installation for IQ.

3.4 Operational Qualification (OQ)

"**O**perational qualification (OQ) is the documented collection of activities necessary to demonstrate that an instrument will function according to its operational specification in the selected environment"[2] Emphasis should be placed on "in the selected environment". Testing of instrument hardware at the user's site is required because instrument characteristics can change when shipped from the vendor to the user, for example through mechanical vibration.

Good to know!

Users, or their qualified designees, should perform OQ tests to verify that the instrument meets manufacturer or users specification in the user's environment (USP <1058>).

The most frequently asked questions related to OQ testing are: what should be tested, which are the acceptance criteria, and who should perform the tests? USP answers all the questions in a single sentence: "Users, or their qualified designees, should perform these tests to verify that the instrument meets manufacturer or user specifications in the user's environment. Designees could be, for example, vendor representatives."

If a system is comprised of several modules, 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. USP does not give a detailed answer on what exactly should be tested: "The extent of testing that an instrument undergoes depends on its intended applications. Therefore, no specific OQ tests for any instrument or application are offered in this chapter".

Our recommendation is to look at the vendor's test procedures as a starting point and to only make adjustments if there is a specific reason. If a laboratory uses the same type of instruments from different vendors, it is more efficient to use the same test procedures for all instruments than to use different ones for different vendor instruments. We also recommend using the same test procedure for a specific instrument throughout the company, independent from the location. This allows comparing instrument performance across the company and facilitates exchange of instruments and analytical methods.

The frequency of OQ depends on the type of instrument, on the stability of the performance characteristics, but also on the specified acceptance criteria. In general, the time intervals should be selected so that the probability is high that all parameters are still within the operational specifications. Otherwise, analytical results obtained with that particular instrument are questionable. Here the importance of proper selection of the procedures and acceptance limits becomes very apparent. For example, if the baseline noise of a UV/Visible detector is set to the lowest possible limit as specified by the vendor, the lamp will have to be changed more frequently than when set at a factor of 5 higher.

Inspectors expect OQ tests to be quantitative. This means that the test protocol should include expected results and actual results. Figure 13 includes an example for recording of test results of a balance. The header includes three control weights and acceptable limits for the weight. The daily protocol records actual weights and the name and signature of the test person.

Good to know!

If a laboratory uses the same type of instruments from different vendors, it is more efficient to use the same test procedures for all instruments than to use different ones for different vendor instruments.

Instrument	BestBalance	
Serial number	55235A	
Maximal weight	110 g	
Control weight 1	10,000 mg	Limit: ±10 mg
Control weight 2	1,000 mg	Limit: ±1 mg
Control weight 3	100 mg	Limit: ± 0.1 mg

Date	Weight 1	Weight 2	Weight 3	o.k.	Test engineer Name	Signature
2/3/06	9999.8	999.9	100.0	yes	Hughes	

Figure 13
OQ test example.

3.5 Performance Qualification

Good to know!

Important for consistent instrument performance are regular preventive maintenance, making changes to a system in a controlled manner and regular testing.

"**P**erformance qualification (PQ) is the documented collection of activities necessary to demonstrate that an instrument consistently performs according to the specifications defined by the user, and is appropriate for the intended use."[2]

Here emphasis is placed on the word 'consistently'. Important for consistent instrument performance are regular preventive maintenance, making changes to a system in a controlled manner and regular testing. The PQ 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 system 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 depends on the criticality of the tests, on the

ruggedness of the instrument and on everything in the system that may contribute to the reliability of analysis results. For a liquid chromatograph, this may be the chromatographic column or a detector's lamp.

In practice, PQ testing can mean system suitability testing or the analysis of quality control samples. This is supported by USP <1058>: "Some system suitability tests or quality control checks that are performed concurrently with the test samples can be used to demonstrate that an instrument is performing suitably." For system suitability testing critical 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 is then compared with a predefined value. If the limit of detection and/or quantitation is critical, the lamp's intensity profile or the baseline noise should be tested. For chromatographic equipment SST tests are recommended in USP chapter <621>[23].

Good to know!

PQ testing can mean system suitability testing or the analysis of quality control samples.

For ongoing quality control checks samples with known amounts are interspersed among actual samples at intervals determined by the total number of samples, the stability of the system and the specified precision. The advantage of this procedure is that quantitative system performance is measured more or less concurrently with sample analyses under conditions that are very close to the actual application. Figure 14 shows a template with examples for a PQ test protocol.

Test	Test Case	Expected Result	Actual Result	Pass/ Fail
Baseline Noise	T10	<0.5 x 10^{-4} AU	<0.5 x 10^{-5} AU	Pass
Resolution between Compound A and B	T11	>2.0		
Tailing factor	T12	<1.3		
Precision of Amount Compound A, 6 Replicate Injections	T13	<1%		
Precision of Amount Compound B, 6 Replicate Injections	T14	<1%		

Figure 14
Documentation of PQ tests.

(Preventive) Maintenance and Repair

Analytical instruments should be well maintained to ensure proper ongoing performance. Procedures should be in place for regular preventive maintenance of hardware to detect and fix problems before they can have a negative impact on analytical data. The procedure should describe:

- The maintenance to be done.
- When it is to be done.
- What should be re-qualified after maintenance is done. For example, a PQ test should always be performed after instrument maintenance.
- How to document maintenance activities.

Instruments should be labeled with the dates of the last and next scheduled maintenance.

Planned maintenance activities should follow a documented instrument maintenance plan. Some vendors offer maintenance contracts with services for preventive maintenance at scheduled time intervals. A set of diagnostic procedures is performed and critical parts are replaced to ensure ongoing reliable system uptime.

Unplanned activities that are necessary in addition to the planned activities should be formally requested by the user of the instrument or by the person who is responsible for the instrument. An example of a request form is shown in figure 15.

Equipment Owner:	
System ID:	
Location of Equipment:	
Requester:	
Date:	
Reason for Maintenance: Describe Observation	
Priority:	High ☐ Medium ☐ Low ☐
Comment:	

Figure 15
Request form for unplanned maintenance.

The reason for the requested maintenance should be entered as well as a priority. All maintenance activities should be documented in the instrument's logbook. A template with examples is shown in figure 16.

Log ID	Date	Type of Maintenance	Person Performing Maintenance	Instrument Owner	Comment
	From To	E.g., routine/ non routine	Printed Name Signature	Printed Name Signature	E.g., recalibrated
	From To		Printed Name Signature	Printed Name Signature	

Figure 16
Maintenance logs.

Good to know!

Defective instruments should be either removed from the laboratory or clearly labeled as being defective.

Defective instruments should be either removed from the laboratory area or clearly labeled as being defective. Procedures should be available for most common problems such as defective UV detector lamps. Procedures should also include information if and what type of requalification is required. Uncommon problems, for example, if an HPLC pump becomes defect without any obvious reason, should be handled through a special procedure that guides users of instruments through the repair process and reinstallation. In this case the impact of the failure on previously generated data should be evaluated.

Change Control

Analytical instruments and systems go through many changes during their lifetime. New hardware modules may be added to enhance functionality, for example, an automated sampling system replaces a manual one for unattended operation. Vendors may change the firmware to a new revision to remove software errors or application software may be upgraded to be

compatible with a new operating system. Or a complete system is moved to a newly designed laboratory. Some changes are also initiated when new technologies are introduced, for example, a standard HPLC pump is replaced by a rapid resolution pump for higher sample throughput.

Any changes to instrument hardware, firmware and software should follow written procedures and be documented. Requests for changes should be submitted by users and authorized by the user's supervisor or department manager and by QA. Before any change request is approved, business benefits should be compared with the risks a change may bring. USP chapter <1058> states: "Implementing changes may not always benefit users. Users should therefore adopt changes they deem useful or necessary and should also assess the effects of changes to determine what, if any, requalification is required".

Good to know!

Any changes to instrument hardware, firmware and software should follow written procedures and be documented.

USP also recommends following the same 4Q model for changes as for initial qualifications. This means:

- Specifications should be updated, for example in case a new automated sampling system replaces a manual one.
- IQ documents should be updated, if a new firmware revision is installed. Installation documents should also be updated when a system is moved to a new laboratory.
- OQ documents with new test cases and test protocols should be added if the software is upgraded with new functionality and,
- PQ tests need to be updated to verify ongoing system suitability of a new rapid resolution HPLC pump.

Before any change is approved and implemented a thorough evaluation should be made if OQ tests should be repeated. Depending on the change, an instrument may need no, partial or full testing of a system.