Selecting Parameters and Limits for Equipment Operational Qualification

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Abstract

While operational qualification (OQ) is a well established term within equipment qualification, users of equipment often get unsure when it comes to implementation. The biggest problem is to find good criteria on how to select procedures and acceptance criteria. Should these be the vendor's specifications or should the users define their own limits, and if so, how ? Should all instruments of the same type have the same values or should these be optimized for each individual instrument ? This article will provide an overall strategy and specific examples for HPLC on how to select procedures and acceptance limits that are based on efficient use of resources, on practicality and the intended use of the equipment.

Introduction

Proper functioning and performance of equipment plays a major role in obtaining consistency, reliability and accuracy of analytical data. Therefore equipment should be properly selected, designed, installed, operated, and the correct function and performance should be verified before and during operation. This process is often called equipment qualification (1-5), which is typically broken down into

- design qualification (DQ) for setting functional and performance specification (operational specification)
- installation qualification (IQ) for performing and documenting the installation in the selected user's environment
- operational qualification(OQ) for testing the equipment to ensure that it meets the previously defined functional and performance specifications
- performance qualification (PQ) for testing that the system performs as intended for the selected application.

These terms have been specified and explained for analytical instruments in numerous recent articles that deal with equipment qualification. For example, the Laboratory of the Government Chemist (LGC) established a Working Group, under the auspices of Eurachem-UK, that developed a guidance on equipment qualification. The group defined the individual qualification terms and gave recommendations on what should be included in each qualification. Results have been published by Bedson and Sargent (1). The Analytical Instrument Association (AIA) has developed a Voluntary Guideline (2) for IQ, OQ and PQ to assist their members in helping their customers to comply with regulatory requirements concerning IQ, OQ and PQ. Huber gave step by step recommendations on what should be included in installation qualification, operational qualification and performance qualification in an article on 'Quality Assurance and Equipment' (3) and in a book on the 'Validation of Computerized Analytical Equipment' (4). The UK Pharmaceutical Analytical Sciences Group (PASG) presented a positioning paper on equipment qualification along with broad guidelines as to what each qualification step should include (5) .

While people now agree on the definition, and also have a good understanding of what this means for simple equipment such as a pH meter or a balance, users of complex equipment are still unsure. The problem does not lie principally in design qualification and installation qualification, but in operational qualification and performance qualification. Frequent questions regarding OQ are:

1. What procedures and test standards should be used: should they reflect the intended use of the equipment or should they be generic for the instrument category ?
2. What should the acceptance criteria be: should they be in line with the manufacturers specifications or should they reflect the intended use of the equipment?
3. Should I use the same procedures and acceptance criteria for all instruments of the same type in my laboratory and/or in our company ?
4. For modular systems: should I test each module, or is it enough to test the system as a whole ?
5. How frequently should the OQ tests be done ?
6. Should the tests be redone after instrument repair or when the instrument is moved to an other lab ?
7. Can/should the test be done by the vendor or by the user ?
8. Can/should I do preventive maintenance before the OQ test ?
9. Why do I need OQ at all, if I use the equipment for one specific application only, isn't performance qualification enough ?

In this paper we give recommendations related to Operational Qualification of equipment hardware. The recommendations reflect the authors' common sense and are based on practical experience. They are not controversary to any standards or official guidelines but complementary. They can be used in those cases where information in official guidelines and standards is insufficient for day-to-day work. References to official guidelines and standards are given where appropriate. While the recommendations can be applied to all analytical equipment, we frequently use liquid chromatography as an example, which is kind of representative for complex instrumentation.

PQ for equipment hardware will be discussed in a later article, as well as OQ and PQ of computers associated with analytical equipment for instrument control and data evaluation.

Purpose of OQ

Before we discuss implementation of OQ, it is important to understand why we do equipment qualification.

1. Firstly, there is no doubt that well-performing equipment is a prerequisite for getting good analytical data. Therefore everyone who is concerned about data quality should perform equipment qualification.

2. There is a second aspect, and this is equally important for those working in a regulated or accredited environment: even though not (yet) directly spelled out in regulations and official guidelines, such as Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP), or in accreditation standards such as the ISO guide 25 or EN 45001, equipment qualification is usually indirectly required by typical statements such as that in the US cGMP regulations (5): ‘Equipment shall be routinely calibrated, inspected and checked according to a written program to assure proper peformance’. The implementation of these requirements is nothing other than equipment qualification. Also, as mentioned earlier, working groups of international organizations such as the EURACHEM (1), and industrial working groups such as the Pharmaceutical Analytical Sciences Group (PASG) (6), are developing guidelines and position papers. Failing to meet regulatory or accreditation standards can have a tremendous impact on a company’s image and business. In light of this, it is important not only to do equipment qualification, but to do it such that the qualification criteria are met as frequently as possible.

3. There may be a third reason: users of equipment may want to know if the equipment they purchased meets the published manufacturer’s specification.

Considerations

What should be the test items, procedures and acceptance limits ?
Before we start with the discussion about test items, test procedures and acceptance criteria, we should have a closer look at the definition made by the LGC/Eurachem working group who defined OQ as

" The process of demonstrating that an instrument will function according to its operational specification in the selected environment"

Another similar definition for OQ came from the US Pharmaceutical Manufacturer's Association (PMA) (7):

"Documented verification that the equipment related system or subsystem performs as intended throughout representative or anticipated operating ranges."

Even though the definition is short and leaves a lot of room for interpretation, one thing becomes obvious: OQ should prove that the instrument is suitable for its intended use. OQ is not required to prove that the instrument meets the manufacturer's performance specifications. This is a frequent misunderstanding and we have experienced that many operators prefer to use the manufacturer's specifications because usually these are readily available.

However, a mistake such as this can have an enormous impact on the equipment's maintenance costs. One example is the baseline noise of a UV/Visible detector: a performance criteria that is important for a method's limit of detection and limit of quantitation.

The baseline noise as offered today by many UV/Visible detectors is in the range of 1 to 2 x 10-5 AU, and much lower than the limit of detection and quantitation required for most applications. This value is achieved under optimum conditions, such as with a reasonably new lamp, an ultra clean flow cell, stable ambient temperature, HPLC grade mobile phase, no micro leaks in the entire HPLC system and so on. These conditions are always valid at the manufacturer's final test and probably at the time of installation in the user's laboratory. However, after some time, optical and mechanical parts deteriorate, e.g., the lamp loses intensity and the flow cell may become contaminated. So, if we repeat the test after 3, 6 or 12 months, the noise of 1 x 10-5 may no longer be obtained.

The question is now, how do we know from which time on the detector was not within the OQ specifications ? An auditor also may ask the question, how do we know that all the data measured in the past are valid, if the instrument was not within the specifications as set by the user. In this case it is therefore necessary to do the OQ tests much more frequently and to change the lamp more frequently, and probably clean the flow cell on a regular basis. This requires additional operator's time and creates costs which can be justified if the application requires such low baseline noise.

They cannot be justified if the instrument is only used for applications that don't require such low baseline noise.

Which test sample should be used: a generic standard or a standard that is specific to the application

Let's assume the instrument is used for different applications, which means different samples, different columns and different calibration standards. In this case it is recommended to use a generic standard for the same instrument category. We would also recommend using the same approach if multiple instruments in a lab perform different applications. If there are just one or two instruments that run one type of application with one calibration standard, it makes sense to also use that standard for OQ.

Should all instruments of the same category pass the same criteria or should each instrument have its own limits?

This is another question that comes up frequently in discussions. For example, you have in your lab HPLC's from different vendors that may also have been purchased at different times. In this case the instruments will have different performance characteristics. For example, the UV/Visible detector's baseline noise has decreased by about a factor of 10 over the last 10 years. There may be instruments in the lab with 1 x 10-4 Absorption Units (AU) and others with 1x10-5 AU. The recommendation is to define 2 x 10-4 as general limits. If there are applications on specific instruments that require a lower baseline noise, select the newer ones to be run for this application and make an exception for the noise limit for this instrument, 2x10-5 AU, for example.

How often should OQ be performed ?

Test frequency is another important question; is this once a month, after several months or once a year ? The answer depends on

- the type of equipment
- the usage of equipment
- the stability of the equipment
- the operational specifications set by the user

The most important criterion here is to make sure that the test frequency has been selected such that the equipment will pass the tests with high probability.

Modular vs. holistic testing ?

Another frequent point for discussion was always whether in a modular system each individual module should be tested (modular testing), or if the system should be tested as a whole (holistic testing). This discussion has been halted suddenly with a published statement by an US FDA field investigator in 1994 (8). The recommendation was, and still is, to use in general the holistic approach: test the system as a whole, and look into individual modules only if the system does not pass. However, this is then more for diagnostic purposes than for test purposes. The same recommendation has been made by the LGC/Eurachem working group (1).

Who should do the test, a representative of the vendor or the user ?

This is both a resource and business question, in addition to the technical aspect. In principle, this can be done by the user and by the vendor. The technical question relates to the procedure the vendor offers: does it really check the critical performance limits of the instrument? For example, we would have some doubts about HPLC procedures that measure a pump's step gradient performance at every ten percent B instead of one percent differences. As long as test procedures relate to the intended use of the instrument, it may be more economical if a vendor does these. The advantage for the user is that he or she does not have to be careful about the traceability of tools such as thermometers, because the vendor's representative supplies everything along. Also, for whatever reason, some auditors prefer to see a calibration stamp on the equipment that comes from outside the user's lab.

Should preventive maintenance (PM) be done before the OQ ?

In our example with the UV/Visible detector lamp, this would solve the problem of not being within specifications due to the lamp aging. The LGC/Eurachem working group recommends doing PM before OQ. It is our experience that some inspectors did not like this procedure. The reason being that there is no evidence that the instrument was performing properly all the time. Before a decision is made, one should think about the purpose of an OQ: is it proof that the equipment did and does perform according to specification all the time, or should it make sure that the equipment is fit just for future work ? The answer to this question will also answer the preventive maintenance question. In light of this, the exact purpose of OQ should be included in the Operating Procedure.

Why should I do OQ at all, isn't PQ enough ?

The final question that arises is: why should I do OQ at all on a regular basis, why is PQ not enough ? This is a valid question for many users. PQ has several advantages: it is done on a more frequent basis, and it is more specific to the user's application. So, if the instrument is used just for one or maybe only a few specific applications, and if the PQ tests include all relevant performance criteria, the regular OQ test may be omitted. The critical question here is which parameters are tested within the PQ test.

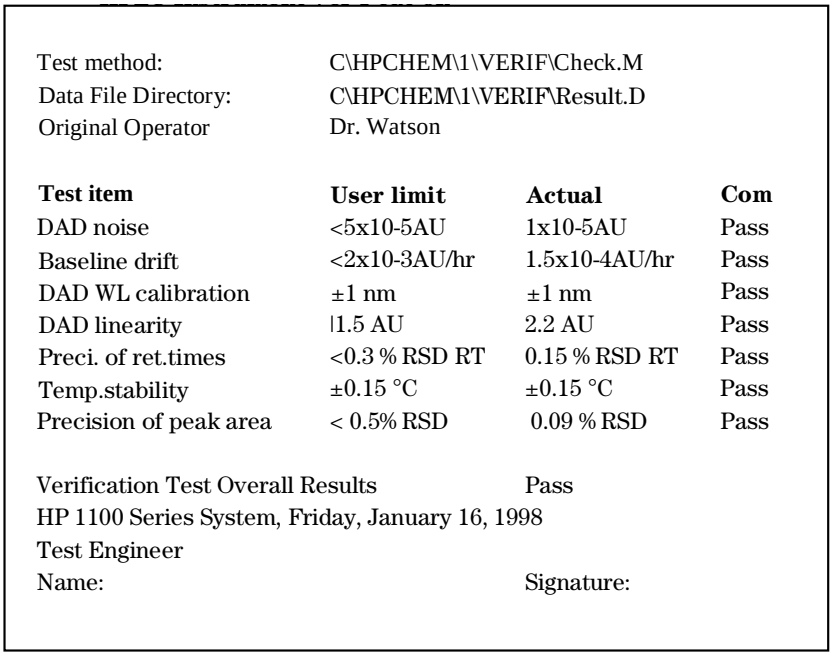
One should also not forget that regular OQ tests provide on-going information on the performance of the HPLC System. Performance trends can be measured and recorded

and can also give an early indication that an instrument may no longer perform as expected in the near future. For example, gradient composition precision is a key factor for the precision of peak retention times and therefore also peak areas. If this parameter is measured and is approaching the limit, the peak retention time precision will also soon exceed the specified limits.

A practical and economical approach for implementation

Several aspects have been discussed in the previous chapter. Now it is relevant to give recommendations for practical implementation.

1. Only use one documented procedure for all instrument categories of the same type in your lab, and preferably within your company. This significantly reduces number of documents and time for training of personnal.
2. For all instrument categories in a laboratory, gas chromatographs for example, use the same OQ procedure and the same test compounds. This makes it easy to compare instruments against each other; new instruments can be compared with existing ones, and it is easier to set specifications for future purchases.
3. For all instruments in a laboratory use the same acceptance limits, independent of the age, brand and actual performance of the instrument.
4. The procedures and the acceptance limits should be selected such that in normal circumstances all instruments pass the test. Therefore the instrument with the worst performance will determine the acceptance limits.
5. If there are applications on specific instruments that require more stringent performance limits for specific applications, make an exception for this instrument and set the limits to the more stringent value.
6. Define the time distance between two OQ's, such that the instrument will pass the test with high probability.
7. Define, in an SOP, the scope of the OQ. For example, should it prove retrospectively and prospectively that the equipment was and will be fit for it's intended use, or should this be done just from now on for the future
8. In case OQ is for future use, plan preventive maintenance before OQ.
9. Always start with the test of the full system (holistic testing). If that test does not pass the criteria, test individual modules.
10. Make a technical and business evaluation on whether to do OQ using your own staff, or by vendor's representatives. If the vendor's procedure does not deviate greatly from your expectations, ask if the vendor can make adjustments.
11. Always ask the vendor for help. Even if you decide to do OQ using your own staff, vendors should still assist you by providing you with test procedures, certified standards for testing and software for automated testing.
12. Generate a test report that includes a table with test items, your acceptance criteria, actual results and a comment if the test passed the criteria. An example is shown in figure 1. Keep this report for regulatory purposes.



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	ǀ1.5 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

Case studies

An example is given here for HPLC Systems tests.

Scenario 1: Pharmaceutical QC lab with 25 HPLC systems.
The systems have been acquired from 3 different vendors over the last 10 years. They are used for compound analysis in the range of 20 to 100%. Three out of the 25 are used for compound analysis and simultaneously for quantitative analysis of impurities down to 0.1 %. They are all equipped with an isocratic pump, with an automated sampler, and with a time programmable variable wavelength UV/Visible detector. The detector's baseline noise manuafcturer's specification varies from 1.5 x 10-5 AU (best) to 1x 10-4 (worst). The instrument's wavelength accuracy varies from +- 1 nm to +- 4 nm. Only systems recently acquired from Hewlett-Packard are equipped with built in holmium oxide filters for wavelength calibration.

A few remarks:

1. An SOP should be developed that will be used for all systems. The test procedures are all the same.

2. The acceptance limits are all the same. The baseline noise spec is 5 times the specification of the worst instrument. This provides enough tolerance in case the condition of the systems is not in ideally matched with new maintenance parts. It also satisfies the needs of most applications run in the laboratory. Only the ones that are used for main compounds and impurities will have a more stringent

acceptance limit of 5x10-5 AU.

3. Even if some units have a built in holmium oxide filter for wavelength accuracy calibration, a certified caffeine standard is injected.

4. 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.

5. The instruments used for quantitative analysis are always calibrated with a chemical standard before and during a series of sample analyses. Therefore the accuracy and linearity of the injection volume does not need to be tested.

6. The OQ procedure should be scheduled once a year.

Parameter	Procedure (*)	User Limit
Leak testing	Flow test by volume or weight/time	± 2.5 %
Baseline drift	ASTM Method E19.09, 20 min	2 x 10-3 AU
Baseline noise	ASTM Method E19.09, 20 x 1 min	2x10-4 AU (or 5x10-5 AU)
Precision of injection volume	6 x injection of caffeine standard, RSD of peak areas	2% RSD
Precision of flow rate	6 x injection of caffeine standard, RSD of retention times	2% RSD
Detector linearity	Inject 5 standards	1.5 AU, 5%
Wavelength accuracy	Certified caffeine standard is injected	± 4 nm
Autosampler carry over	Injection of blank solvent after large concentration	0.3 %

(*) For detailed procedure, see reference 9

Table 1. Test parameters and acceptance criteria for case study 1.

Scenario 2: Environmental testing lab equipped with 1 HPLC system
The HPLC system is an HP1100 Series HPLC system with a quaternary pump, column compartment, automated sampler with 100 vials, diode-array detector and a ChemStation. The system is intended to be used mainly for the analysis of phenyl urea herbicides in drinking water. The limit of quantitation is 50 ppt. With an injection volume of 50 ❍l this results in a peak height of about 100 mAU. The DAD has built in holmium oxide filter for wavelength verification. The specification for baseline noise is 2 x 10-5 AU.

A few remarks:

1. For wavelength calibration we recommend using the built in holmium oxide filter

2. We recommend setting the limit for the baseline noise of the UV/Visible DAD to 6 x 10-5 AU. This is 3 times higher than the instrument specification. This provides enough tolerance in case the condition of the systems is not in ideally matched with new maintenance parts.

3. The OQ procedure should be scheduled once a year. Because the detector's baseline noise is critical for the success of the application, this test should be scheduled every month.

4. As long as the instrument is used for pesticides only, a pesticide standard compound, e.g., triazine, can be used for flow precision, injection precision and for a linearity test, if a suitable certified standard is available.

5. The instrument is always calibrated with a chemical standard before and during a series of sample analyses. Therefore the accuracy of the injection volume does not need to be tested.

Parameter	Procedure (*)	User Limit
Leak testing	Flow test by volume or weight/time	± 2.5%
Baseline drift	ASTM Method E19.09, 20 min	2 x 10-3 AU
Baseline noise	ASTM Method E19.09, 20 x 1 min	6 x 10-5 AU
Precision of injection volume	6 x injection of caffeine standard, RSD of peak areas	1 % RSD
Precision of flow rate	6 x injection of caffeine standard, RSD of retention times	1 % RSD
Detector linearity	inject 5 standards	1.0 AU, 5%
Wavelength accuracy	holmium oxide filter	± 2 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	< 0.3 %
Mobile phase composition accuracy	Step gradients from 4 to 7 % B, step heights relative to 100%, with acetone tracer	± 1 %
Mobile phase composition ripple	Peak to peak noise at 4, 5, 6 and 7% B	0.2 %

(*) For detailed procedure, see reference 9

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

Conclusion

Operational qualification is an important part of the overall equipment qualification process. The careful selection of test items, the test procedures and acceptance limits is extremely important, because if set too stringently, the instruments' test may have an unnecessarily high failure rate and/or the maintenance efforts will be too high. If the limits are too relaxed, the equipment will not prove itself fit for its purpose. While individual test procedures and limits are specific for each instrument some more general recommdenations apply to all types of equipment:

1. Use generic chemical standards for testing, if the equipment will be used for several different applications. Use applications specific standard, if the instrument will be used for one application only
2. If there are multiple instruments of the same category in a lab, use the same procedure and acceptance limits for all instruments
3. Set the acceptance limit higher than the manufacturer's specification. This may be up to a factor of 5 or 10. For those instruments that require more stringent values to demonstrate their fitness for the intended use, an exception should be made, and the limits should be set to more stringent values.
4. For modular sytems, test the system as a whole and not module by module.
5. Set the time intervalls between two OQ's such that the actual test results in general are at least still 30% away from the limits.
6. If the vendor offers OQ services, make a business evaluation on whether OQ by the vendor or the user's firm will be more cost effective.

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