

SYSTEM SUITABILITY

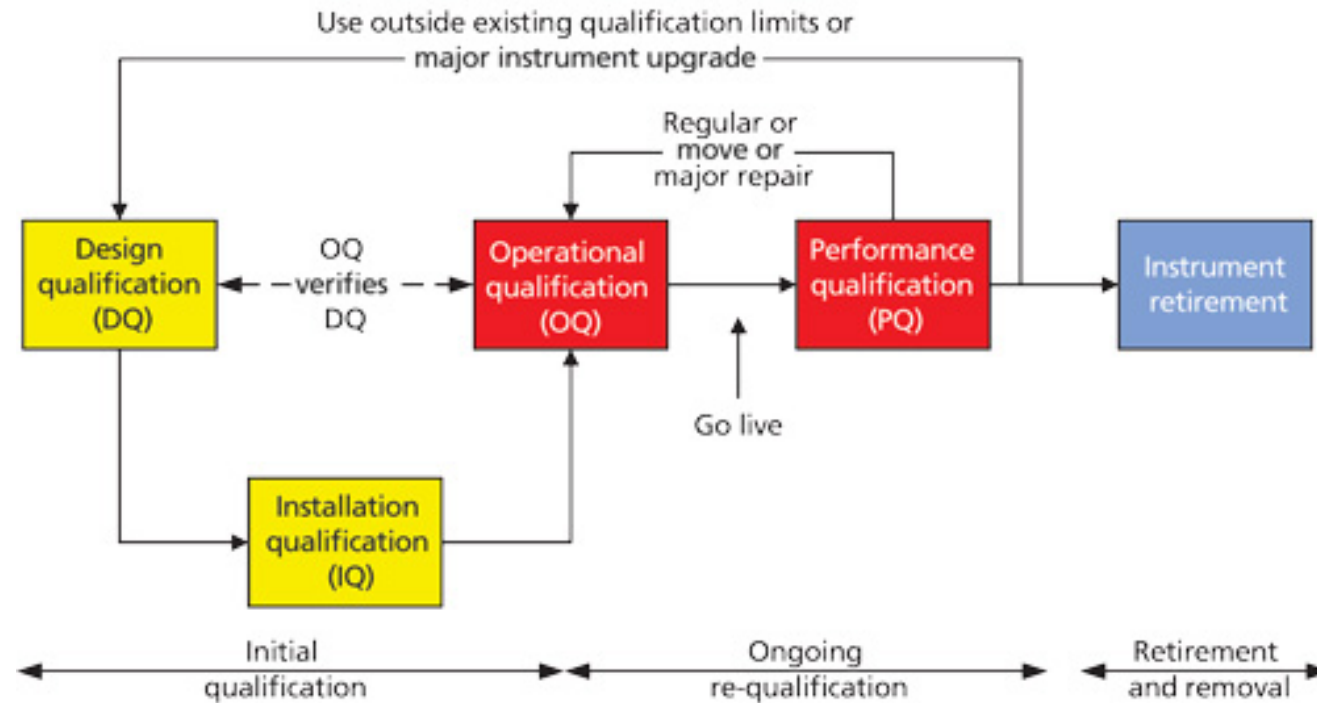
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BUT BEFORE THERE WAS SYSTEM SUITABILITY THERE WAS:

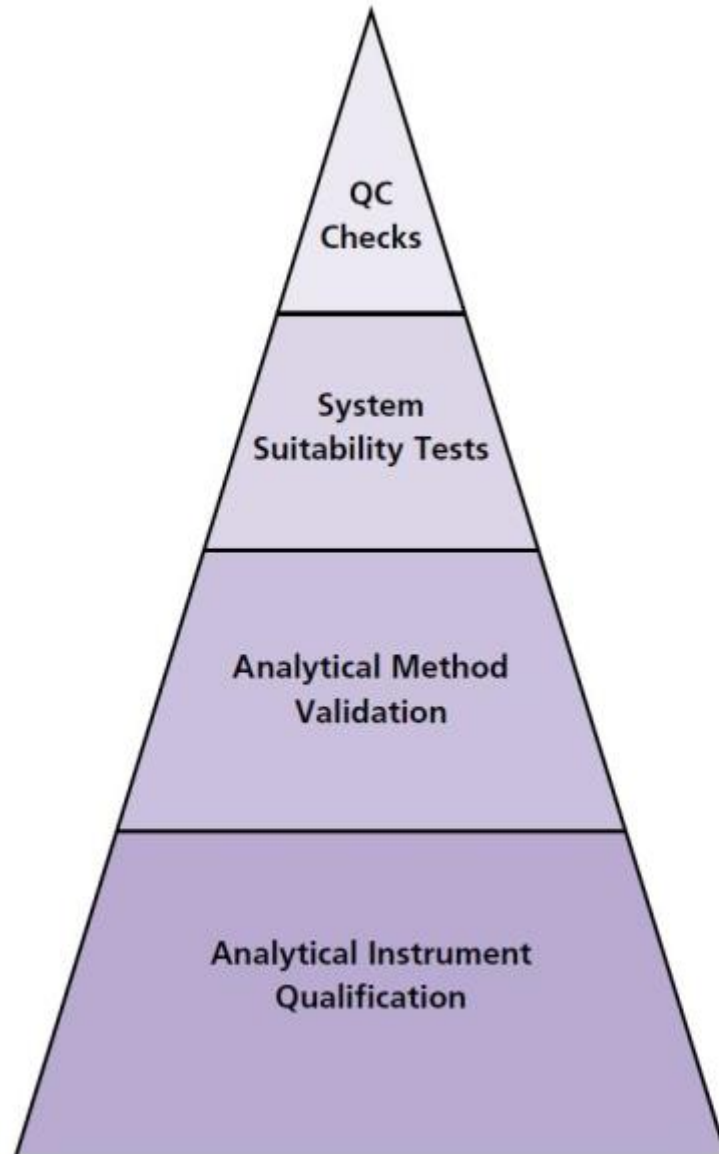
ANALYTICAL INSTRUMENT QUALIFICATION(AIQ)

- Design Qualification (DQ) is used to define the user's requirements before purchasing an instrument or system.
- Installation Qualification (IQ) demonstrates that the components have been correctly installed.
- Operational Qualification (OQ) shows that the installed system meets the user specification. A periodic OQ is performed as well as after major maintenance or service of an instrument.
- Performance Qualification (PQ) demonstrates that the system continues to perform as defined.

United States Pharmacopeia Chapter <1058> on Analytical instrument qualification (AIQ)



The Data Quality Triangle (Modified from USP <1058> on AIQ)



Instrument or Method?	When Performed?	Controls What?
Method	<ul style="list-style-type: none"> • During an analytical run 	<ul style="list-style-type: none"> • System drift over the time of the analytical run and over time of all runs • Can identify system-to-system bias
Method	<ul style="list-style-type: none"> • On the day of analysis • Before committing samples for analysis 	<ul style="list-style-type: none"> • Confirmation that the system (instrument and method combination) functions within predefined limits
Method	<ul style="list-style-type: none"> • Before application of the method 	<ul style="list-style-type: none"> • Confirmation of method operating parameters • Sample preparation • Operator-to operator bias • Instrument-to-instrument bias • Method transfer between laboratories
Instrument	<ul style="list-style-type: none"> • At initial instrument set up • At regular intervals thereafter • Following major maintenance 	<ul style="list-style-type: none"> • Instrument capability • Calibration of instrument independent of method or operator and traceable to national standards whenever possible

Within the analytical community, system suitability is sometimes confused with the operational qualification performed during instrument IQ/OQ/PQ.

Operational qualification is used to demonstrate that all components of the instrument, and/or the complete instrument system, are meeting performance standards (i.e., specifications).

System suitability tests (SSTs) can NOT be used to qualify an instrument. Using SSTs as the sole instrument qualification approach will leave any laboratory exposed to regulatory action as the instruments and systems cannot be demonstrated as being fit for their intended purpose.

The testing methodology for operational qualification is specific to instrumental performance. In order to ensure that the chromatographic system is tested in a manner not affected by the analytical method, the system is usually qualified in a well-controlled environment. Therefore, the analytical HPLC column is removed in order to remove its contribution to the variability of the system, and a simple mobile phase should be used in the OQ of HPLC systems.

Is the instrument fit for purpose over defined operating ranges?

The foundation of all analytical work and the quality of the data: do you believe your instrument?

Instrument qualification must be independent of an analytical method and should use calibrated and traceable test equipment and standards. The AIQ process requires the laboratory to define the operating parameters over which the instrument will operate and then using appropriate tools and reference materials will confirm that the instrument can operate to the required specification:

- A balance must use calibrated weights that are traceable to national or international standards
- A pH meter should use buffers prepared from appropriate reference source (from an appropriate NIST or equivalent)
- A pump for a liquid chromatograph will use a calibrated digital flow meter to measure the top and bottom flow rates

This lays the foundation for all other work in the data quality triangle. To be effective it must be independent of the analytical method. The qualification focuses on the instrument and not the method.

One positive impact of AIQ is that it should ensure effective and efficient technology transfer (method validation); because performance differences between instruments will be determined.

Why a system suitability test cannot replace analytical instrument qualification?

Again lets focus on the instrument function tests performed during the operational qualification (OQ) phase of the AIQ.

A typical argument about using SSTs in place of AIQ goes something like this:

“Our laboratory does not need to qualify the instrument because we run SST samples and they are within limits.”

There are a number of problems this argument but USP <1058> analytical instrument qualification process section states”

Operational Qualification & Instrument Function Tests:

Instrument functions required by the user should be tested to verify that the instrument operates as intended by the manufacturer... Users, or their qualified designees, should perform these tests to verify that the instrument meets manufacturer or user specifications in the user’s environment.

In essence, this means that the functions of an instrument must be tested. Using a liquid chromatograph as an example, the flow rate of the pump and the wavelength accuracy of the detector are just two of the parameters that can be tested at a modular level. Flow rate would use a calibrated and traceable digital flow meter. Wavelength accuracy using a sample containing a series of very sharp peaks such as a solution of holmium oxide. These are some of the modular tests that can be applied to the components of a liquid chromatograph but there should also be a check that the overall system works correctly as well.

Your firm has not conducted adequate calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing limits for accuracy and precision [21 CFR § 211.160(b)(4)]. For example:

Your firm failed to conduct injector and detector performance testing for the HPLC system. For example, no HPLC injector and detector testing for linearity, accuracy, and precision were conducted, such as:

- 1. various injection volumes and standard concentration testing;*
- 2. evaluation of detector for noise/drift; and*
- 3. Carryover*
- 4. No established written program for the maintenance and calibration of instruments such as the atomic absorption and HPLC instruments and the [redacted] balance used for drug analysis.*
- 5. Failure to have a complete calibration program for the HPLCs in that the gradient accuracy and detector linearity are not being verified.*

Note the type of qualification testing required in these warning letter examples: e.g. gradient pump accuracy, autosampler injection volume accuracy and precision as well as detector linearity. These are not tested in system suitability which focuses on method specific parameters such as retention time windows, peak shape and resolution between peaks of interest as well as column performance. There is also the need for equipment to be calibrated against national or international standards whenever possible.

The message here is very clear – ensure that the instrument or system has been qualified and / or calibrated as necessary as it is the foundation of all further analytical work. Failure to qualify may result in poor quality analytical results and can give problems when transferring analytical methods to other laboratories. Many of us have experienced method transfer projects that failed their acceptance criteria due to variance in results directly attributable to performance differences between the instruments used in the originating and establishing laboratories.

“Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.”

System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such. System suitability test parameters to be established for a particular procedure depend on the type of procedure being validated.

The purpose of the system suitability test is to ensure that the complete testing system (including instrument, reagents, columns, analysts) is suitable for the intended application.

Some guidelines indicate that SST must be performed before (initial) and throughout all regulated assays. It is no longer sufficient to assume that the system will function properly during the experiment after passing initial SST.

In addition, the use of a single component calibration solution to check system suitability is not adequate because the system's separation capabilities are not demonstrated. Rather, the use of system suitability samples or resolution test mixtures containing both main components and expected impurities is required. For impurity testing, it is customary to include one of the several key impurities in SSS to demonstrate resolution and system sensitivity.

If initial SST fails, the analyst should stop the sequence immediately, diagnose the problem, make necessary adjustments or repairs, and re-perform SST. Analysis of actual sample should commence only after passing all SST limits, not only the failed criteria. Most SST failures are traced to problems from the autosampler, pump, column, mobile phase or human error. If one of the SSS injections fails, data from all samples after the last passing SSS become invalid and must be repeated.

System suitability is not calibration!

System suitability is “the process of validating whether your is acceptable for providing useful analytical data without any bias.”

Retention time is one of the easiest measurements to make and track in an LC run. It is also important that retention time be fairly constant because the data system uses retention time to identify peaks; peaks that drift outside a certain retention time window might not be reported by the data system.

It may vary from one nominally identical instrument set-up to another. For system suitability, it is good to set a retention-time window as specified in the method. This will allow for some variation in mobile-phase composition from batch to batch or a gradual change in column characteristics.

Resolution, the separation between two peaks, is one of the most critical system suitability parameters. System suitability, in one way of thinking, is a mini validation that shows that the method is still valid for use. Usually, separation of one or more key peaks from other peaks is the objective of an LC method.

Selecting resolution as a system-suitability parameter is one way to ensure that the critical separation is possible under the current conditions. Setting an easily attainable “resolution greater than” specification allows more flexibility than stating a specific value of resolution that might be difficult to obtain.

Response, in terms of peak height or area, might or might not be an important systems suitability parameter to include in your tests. If your method is a stability-indicating assay, bioanalytical method or other method that must detect trace concentrations of analyte, you need assurance that you can reach the detection limits necessary. In this situation, a system-suitability test should include one or more injections at the lower method limit.

The limit of detection (LOD), lower limit of quantification (LLOQ), and signal-to-noise ratio (S/N) all relate to the quality of the detector signal at low concentrations of sample. This is another way to look at detector response. If the method is used for trace analysis, such as a stability indicating assay, an impurities assay or a bioanalytical assay, it is important to ensure that the method performs at the lower end. Methods that fall in this category often include one or more samples at the lowest concentration of interest to verify the LOD, LLOQ and S/N.

Many people include a column plate number as part of a system-suitability requirement. Some do not consider the plate number as a diagnostic. Peak response and resolution are critical parameters that depend indirectly upon plate number so if you have these parameters as part of your test, there is not much point in measuring the plate number.

For gradient methods, plate numbers are difficult to determine and a peak width at half-height might be a more appropriate parameter. If you choose to include the plate number as a suitability parameter, be liberal with the requirement so that normal column deterioration can occur without failing suitability or you will end up replacing columns with plenty of useful life left.

Tailing peaks can destroy a separation and reduce sensitivity below required levels. They can also be good indicators of column deterioration or errors in mobile-phase preparation. In other instances, peak tailing might not be very important, such as when only one or two peaks are present and excess resolution exists. If the peaks in your separation tend to tail and this will have a negative impact on the method performance, include a tailing factor requirement in the system-suitability test.

Precision measurements define how reproducible the results are and give you confidence in the data you will gather. If the method uses external standardization, precision measurements assure that the autosampler is delivering the same volume each time and that sample preparation provides a consistent yield. When internal standardization is used, the internal standard will compensate for some instrument imprecision and a precision measurement might not be necessary. Generally, six replicate injections will give you a very good idea of the precision of the method.

Accuracy is the measurement of how close an experimental value is to the true value. Running a standard curve at the beginning of a run sequence or injecting replicate standards for a single-point calibration will establish the accuracy of the method. Because this is normally part of the method itself, accuracy is often not included in system suitability.

Samples that do not contain any analyte can be used to determine carryover and confirm reagent purity. Such samples are often injected immediately following a high concentration standard to measure carryover. Depending upon their purpose, blank samples can comprise a blank extracted matrix, selected reagents or just the injection solvent.

For the Assay in a drug substance monograph, where the value is 100% for the pure substance, and no maximum relative standard deviation is stated, the maximum permitted %RSD is calculated for a series of injections of the reference solution

$$\%RSD = KB\sqrt{n}/_{90\%,n-1}$$

Where K is a constant (0.349), obtained from the expression $K = (0.6/\sqrt{2}) \times (t_{90\%,5}/\sqrt{6})$, in which $0.6/\sqrt{2}$ represents the required percentage relative standard deviation after six injection for $B = 1.0$; B is the upper limit given in the definition of the individual monograph minus 100%; n is the number of replicate injections of the reference solution ($3 \leq n \leq 6$); and $t_{90\%,n-1}$ is the Student's t test at the 90% probability level (double sided) with n-1 degrees of freedom.

RELATIVE STANDARD DEVIATION REQUIREMENTS

Unless otherwise prescribed, the maximum permitted relative standard deviation does not exceed the appropriate value given in the table of repeatability requirements. This requirement does not apply to tests for related substances.

RELATIVE STANDARD DEVIATION REQUIREMENTS

	Number of Individual Injections			
	3	4	5	6
B (%)	Maximum Permitted RSD			
2	0.41	0.59	0.73	0.85
2.5	0.52	0.74	0.92	1.06
3	0.62	0.89	1.1	1.27

Replicate injections of a standard preparation or other standard solutions are compared to ascertain whether requirements for precision are met. Unless otherwise specified in the individual monograph, data from five replicate injections of the analyte are used to calculate the relative standard deviation, %RSD, if the requirement is 2.0% or less; data from six replication injections are used if the relative standard deviation is more than 2.0%

Regulatory issues in a laboratory can be quite complex, involving rigorous testing, meticulous documentation, sound scientific judgment, and proper interpretations of regulations to achieve compliance. No argument can be made against strict regulatory compliance in production facilities used to manufacture and release drug products for public consumption.

However, since the interpretation of the regulation is somewhat inexact and often subjective, the amount of work and documentation required by many organizations has escalated significantly in recent years. Maintaining regulatory compliance has become extremely costly and time consuming.

A case in point is in equipment and software validation, which can often take months to complete and generate hundreds of pages of documentation. While these details may be warranted for the qualification of equipment employing new technologies, most would agree that they might be less meaningful for an off-shelf instrument such as a UV spectrometer from a reputable vendor.

In response to streamline productivity for faster time to market of new drugs, a delicate balance of laboratory productivity and compliance must be achieved. Many research facilities now adopt a two-tier or risk-based approach, allowing less compliance requirements in laboratories for early-phase development (drug discovery, pre-clinical) and full cGMP or GLP compliance for late-stage development.