WHITE PAPER

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Why System Suitability Tests Are Not a Substitute for Analytical Instrument Qualification

Purpose

This white paper discusses the role of System Suitability Tests (SSTs) in the context of Analytical Instrument Qualification (AIQ) and is based upon the United States Pharmacopoeia (USP) general chapter 1058 on AIQ[1]. We will discuss why SSTs are not a substitute for AIQ for the initial qualification or re-qualification (i.e. a periodic, typically annual Operational Qualification) of an instrument.

Introduction

There is a common misconception in some regulated laboratories that system suitability tests (SSTs) can be used to qualify an instrument. This is wrong. Furthermore 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.

USP <621>[2] and European Pharmacopoeia (EP) chapter 2.2.41[3] have both specified requirements for SST for chromatographic analysis to demonstrate that a chromatograph is fit for the analysis it will undertake on the day of analysis. System suitability tests are run each time an analysis is undertaken and each SST is specific for an individual method with pre-defined acceptance criteria e.g. precision, peak shape and resolution from other analytes. If an SST fails, then the samples cannot be assayed. The principle of a point of use check, such as an SST, is applicable to any analytical instrument or system and this is performed just before an analysis to demonstrate correct performance e.g. a check weighing for an analytical balance or a scanning a known standard for an NIR identity check.

Although this white paper is written primarily from the perspective of Good Manufacturing Practice (GMP) regulations and the USP <1058> general chapter on AIQ, the content is good analytical science and applicable to all laboratories.

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An Overview of USP <1058>: Analytical Instrument Qualification

The general chapter on AIQ (USP <1058>) comprises six major sections:

- Components of data quality
- Analytical instrument qualification process
- Roles and responsibilities
- Software validation
- Change control
- Instrument categories

The key sections from USP <1058> that concern our debate of AIQ versus SST are the components of data quality and the analytical instrument qualification process. USP <1058> quotations used in this white paper come from these two sections.

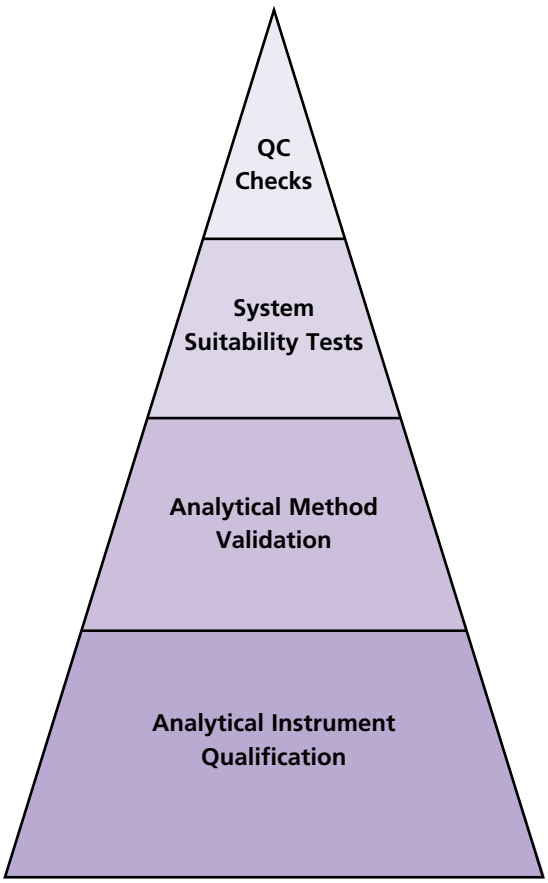
Understanding the Data Quality Triangle

The first major section of USP <1058> is entitled 'Components of Data Quality'. This discusses the four layers, presented in the form of a triangle. Throughout this white paper we will refer to this as the data quality triangle and this is shown in Figure 1.

The purpose of the data quality triangle is to ensure that data quality is ensured with the proper application of these four areas:

- Analytical Instrument Qualification (AIQ)
- Analytical Method Validation
- System Suitability Tests
- Quality Control Check Samples

This approach is applicable to all laboratories regardless of whether they operate in a regulated or quality environment as it describes good analytical science as well as good business by protecting the investment. How many of you would dare ask your manager to buy an instrument that was not fit for purpose? Yet, if you do not satisfy the four layers of <1058>, there is a risk that the instrument will not be suitable. The <1058> data quality triangle has been modified and is presented in Figure 1; we will look at each of these layers in turn and discuss why they are arranged in such an order. We will focus on AIQ and SST layers as these are the main focus of this white paper but mention method validation and QC checks in passing for completeness.



Instrument or Method?	When Performed?	Controls What?
Method	• During an analytical run	• System drift over the time of the analytical run and over time of all runs • Can identify system-to-system bias
Method	• On the day of analysis • Before committing samples for analysis	• Confirmation that the system (instrument and method combination) functions within predefined limits
Method	• Before application of the method	• Confirmation of method operating parameters • Sample preparation • Operator-to operator bias • Instrument-to-instrument bias • Method transfer between laboratories
Instrument	• At initial instrument set up • At regular intervals thereafter • Following major maintenance	• Instrument capability • Calibration of instrument independent of method or operator and traceable to national standards whenever possible

Figure 1. The Data Quality Triangle (Modified from USP <1058> on AIQ)

Instrument Based

Is the instrument fit for purpose over defined operating ranges?

This is the foundation of all analytical work and is a major contributor to the quality of the data: do you believe your instrument? Therefore 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 used 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 is the foundation of all other work in the data quality triangle. To be effective it must be independent of the analytical method. As we shall see in more detail later 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.

The Foundation: Analytical Instrument Qualification

USP <1058> describes analytical instrument qualification as the process for ensuring that an instrument is suitable for its intended purpose. This is the lowest level of the data quality triangle shown in Figure 1 and is the foundation for all other stages of analytical work. It applies to all analytical measurement. The end result of the AIQ process answers the question do you have the right system for the right job? The AIQ process is broken down into four phases, known as the 4Qs model:

- 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

Note that the term performance verification (PV) is not used in USP <1058> or this document, as performance qualification (PQ) is the preferred term.

What happens if you don't qualify your equipment? As Avalone in Crowther and Miller[4] notes one area that is frequently cited in FDA 483 observation reports is the failure to calibrate and maintain laboratory equipment and this is borne out in just three of many warning letters for the laboratory:

The inspection revealed that your laboratory equipment calibration program is inadequate in the following ways:

a. Failure to have written procedures describing specific calibration instructions and limits.
b. Failure to maintain complete calibration records in that they do not include all raw data.
c. Failure to have a complete calibration program for the HPLCs in that the gradient accuracy and detector linearity are not being verified.
d. Failure to conform to the USP <41> for weight and balance determination. The inspection revealed that erroneous values are being used to perform the minimum weight studies.

[ChemSource warning letter, November 2002]

Failure to comply with the General Requirements of Subpart I. Laboratory Controls, as required by 21 CFR 211.160, in that there is:
a. 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.
b. No certification to a recognized standard for the weights set used for checking the [redacted] balance.

[Earlham College warning letter July 2002]

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:

a. 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 testing.

[Ion Laboratories Warning letter July 2009]

Note well 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 – hence the citation of Earlham College for failing to use weights calibrated to a recognised standard.

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.

Analytical Method Validation

The next stage up the data quality triangle is analytical method validation and this, not surprisingly, is method based. Method validation relies on the fact that the instrument is qualified and works correctly; the corollary is that methods developed and validated on unqualified equipment can raise fundamental questions over the quality of the data. The overall method variance may be higher and may have less robustness compared with data generated from qualified instruments.

System Suitability Test

The third layer of the data quality triangle is the system suitability test. Again the basis for a SST working reliably is that the instrument is qualified and the method used is validated. USP <1058> defines this as "Verify that the system will perform in accordance with the criteria set forth in the procedure." This really means is the method running on the system working as you expect on the day you want to analyse samples and before the samples are committed for analysis? This approach is good analytical science and this should be the driver to do this rather than compliance with regulations.

Quality Control Checks

The apex of the data quality triangle is the quality control checks. Again these are method based checks to ensure that the analytical system works throughout the run within predefined limits. Typically these are independently prepared samples of known concentration or amount analysed as unknown samples to confirm that the instrument and method works correctly.

Why SSTs Are Not AIQ

Let us turn back to the subject of this white paper and look at why a system suitability test cannot replace analytical instrument qualification. We will 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 and fallacies with this argument but rather than make our own arguments why this is so, we will use quotations from the USP <1058> analytical instrument qualification process section to do this on our behalf and provide additional comments.

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. This will use a calibrated and traceable digital flow meter. These are some of the modular tests that can be applied to the components of a liquid chromatograph but there should also be a holistic test that checks that the overall system works correctly as outlined by Furman et al.[5]

Method Based

Is the analytical system working on the day?

System suitability tests are method specific rather than instrument specific test to decide if the analytical system is fit to use immediately before committing the samples for analysis.

Although the SST terminology is derived from chromatography (USP <621>), other good examples of SST or point of use checks are the minimum weigh criteria for balances in USP <41> and checking of pH meters with standard calibration solutions of known pH.

The explicit statement that destroys the argument for SSTs replacing AIQ is also found in the same section of USP <1058>:

Routine analytical tests do not constitute OQ testing.

Let us interpret this statement carefully. Routine analytical tests, system suitability test injections and quality control check samples are in the top two layers of the data quality triangle of Figure 1. These are based on a specific analytical method and do not test any explicit instrument parameter. Specifically, as shown by the quotation below:

OQ tests are specifically designed to verify the instrument's operation according to specifications in the user's environment.

This is reiterated by the USP's <621> on chromatography

To ascertain the effectiveness of the final operating system, it should be subjected to a suitability test prior to use. The essence of such a test is the concept that the electronics, the equipment, the specimens and the analytical operations constitute a single analytical system, which is amenable to an overall test of system function.

Note the phrasing used here – an SST is overall test of system function. This is a point of use check that is run on the day rather than showing that the instrument is fit for its full intended purpose. However you must also be aware that in HPLC many examples have been found of SST passing its criteria while in fact the instrument is out of specification for wavelength accuracy, flow accuracy, injection volume accuracy or temperature control accuracy[6].

As an SST cannot check these fundamental HPLC characteristics it fails totally as a substitute for a proper AIQ test and report which does qualify or calibrate these parameters. So to claim that an SST is AIQ is a futile argument: an SST is method based and can only check if a specific method is working. If in doubt look at the tests identified in the example warning letters presented earlier in this paper.

Conclusions

In this white paper we have shown that the role of analytical instrument qualification is to demonstrate that the instrument is fit for purpose across the operating ranges determined by the laboratory. This must be done before any methods are established or samples are assayed. Failure to qualify your instrument effectively (using test equipment that is calibrated to national or international standards) means that the remainder of the data quality triangle is meaningless and the results generated are questionable at best.

In contrast, a system suitability test is a point of use check to confirm that the instrument and the analytical method are working correctly just before the analysis begins. As such, an SST is totally dependent on the instrument having been qualified. An SST cannot be a substitute for AIQ as it is method and not instrument based.

Failure to follow this advice and choosing to rely on system suitability tests to qualify your instrument not only leaves you at risk of regulatory action but also significantly reduces the trustworthiness of your analytical results.

References

[1] USP <1058>

[2] USP <621>

[3] EP Chromatography chapter 2.2.41

[4] H. Avallone, Laboratory Controls and Compliance, in "Analytical Chemistry on a GMP Environment", Ed J. B. Miller and J. B. Crowther, ISBN 0-471-31431-5 Crowther & Miller section 2.3.5 page 41 (2000)

[5] W. B. Furman, T. P. Layloff and R. T. Tetzlaff, J. AOAC Int., 1994, 77(5), 1314

[6] P. Coombes, Laboratory Systems Validation Testing and Practice 2002 ISBN Number: 1930114486

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