White Paper

Deciphering VVQ — How Validation, Verification and Qualification Affect TOC Analyzers

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With cleaning validation the fundamental question is, "How clean is clean?" With Total Organic Carbon (TOC) instruments and methods, the question is whether to perform validation, verification, or qualification. Part of the question is not necessarily which mode to use, but more importantly, "Does the method or instrument 'suit' its purpose?" Currently in the pharmaceutical industry the TOC method can be used for both compendial (USP <643>) and analytical method purposes.

The U.S. Food and Drug Administration (FDA) continues to issue new guidance and updates through regulatory communities and bodies. The United States Pharmacopeia (USP) continues to update its general chapters <1058> Analytical Instrument Qualification, <1225> Validation of Compendial Methods, and <1226> Verification of Compendial Methods to further reflect implementation of the International Communities of Harmonization (ICH) guidelines, and consensus standard groups like ASTM and the International Organization for Standardization (ISO). All this new information can lead to greater confusion in the highly regulated pharmaceutical industry. Rather than create greater confusion, this paper is intended to demonstrate what mode (validation, verification, or qualification) of choice should be used for TOC instrumentation or the methodology.

Validation, Verification or Qualification?

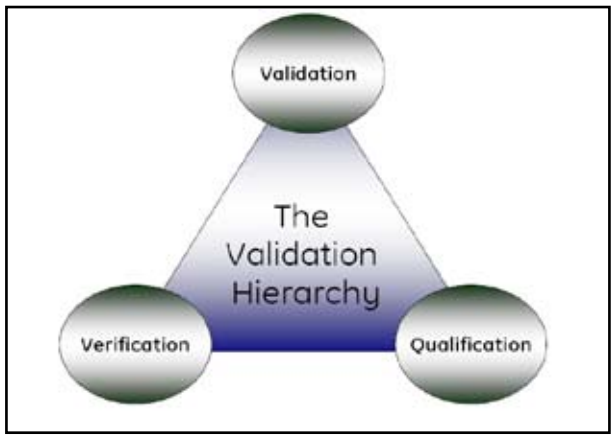
To keep it simple, processes are "validated" and instruments are "qualified." Verification is a more recent term that refers to the suitability of a *compendial procedure* under actual conditions of use.[1] That said, however, ISO considers validation as a confirmation through the provision of objective evidence that the requirements for a specific *compendial method's* intended use or application have been *fulfilled*.[2] Verification is the confirmation through the provision of objective evidence that *specified requirements* have been fulfilled (e.g. cleaning validation or method development).[3] Put simply, if you are using a compendial method, you *verify*; a non-compendial or alternative analytical procedure, you *validate*. Qualification, on the other hand, is specific to instrumentation, and most certainly production equipment and water systems. Analytical Instrument Qualification (AIQ) provides documented evidence that the instrument performs suitably for its *intended purpose* and that it is properly maintained and calibrated.[4]

This may sound confusing, but let's look at one critical element — the intended purpose of the methodology or instrumentation — and the various hierarchies associated with validation, verification, and qualification.

Distinct Components of Validation

Verification methods, qualification methods, software, production processes, cleaning methods or sampling procedures, and system suitability[5] all contribute to the make-up of the "Validation" Hierarchy. Although many pharmaceutical companies use the terms qualification, verification, and validation interchangeably, verification and qualification are actually two subcomponents of validation. All equipment requires qualification, and all processes require verification, but not all processes require validation. If a process is to be validated, the system, the software, and the method *must* all be validated, and then *system suitability* is executed periodically to keep a process in check.

In early 2007, USP proposed revisions to the method validation guidelines published in Chapter <1225>.[6] For the most part, the revisions were made to continue to harmonize with the ICH Analytical Method Guideline known as ICH Q2 (R1). USP <1225> and ICH Q2 (R1) rec-



ommend the validation of specific parameters including, but not limited to: accuracy, precision, linearity, specificity, limit of quantitation and detection, analytical range and robustness. However, it is important to note that ICH Q2 (R1) includes *system suitability* as a key parameter to be evaluated during analytical method validation. The guideline indicates that system suitability 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. The guideline also states that system suitability test parameters should be established for a particular procedure or method based upon the type of procedure or method being *validated*.[7]

Using the TOC method for an application like cleaning validation or verification requires that the TOC methodology be treated and validated like an analytical method. It is true, however, that TOC is also a pharmacopeial method, and some believe that a pharmacopeial method does not require separate method validation. Some even claim that separate method validation is not required because USP Chapter <643> is perceived as a "validated" analytical method. Certainly, it is the case that TOC is a USP method and can be used for both a compendial method and an analytical method. However, the fact that TOC is a USP method simply means that TOC is a "suitable" method for measuring TOC in purified water (PW) and in water for injection (WFI), if this is the intended purpose of the methodology. It does not indicate that TOC is a *validated* method for measuring an organic Active Pharmaceutical Ingredient (API) in water or on a swab for a cleaning validation protocol or study. Therefore, it is encouraged that the TOC method be validated following ICH Q2 (R1) guidelines if used for cleaning validation samples.

Distinct Components of Verification

It generally has been assumed that USP methods are validated, but not knowing what might have signified validation in the past can lead pharmaceutical laboratory personnel down an ambiguous path. USP Chapter <1225> does not provide any guidance on how to verify procedures in the absence of a full validation protocol. This new chapter summarizes what is necessary to confirm that the *compendial* procedure or method works for a particular drug substance, excipient, cleaning agent, or dosage form by *verifying* a subset of validation characteristics rather than completing a full validation study or protocol. Chapter <1226> is considered an extension of Chapter <1225>, and both chapters use similar terminology.

The intent of <1226> is to provide guidance on how to verify that a *compendial* procedure being used for the first time will yield acceptable results "under the actual conditions of use," which means utilizing the laboratories' or operations' personnel, equipment, and components. Compendial method verification consists of assessing selected analytical performance characteristics such as accuracy, precision, and limit of detection [as mentioned above and described in Chapter <1225>, or ICH Q2 (R1)] to generate appropriate relevant data, as opposed to repeating the entire validation process. The verification process comprises six components: compendial methods, laboratory personnel, approved procedures or protocols, data comparison, acceptance criteria evaluation, the final summary or justification documentation, and corrective action, if necessary.

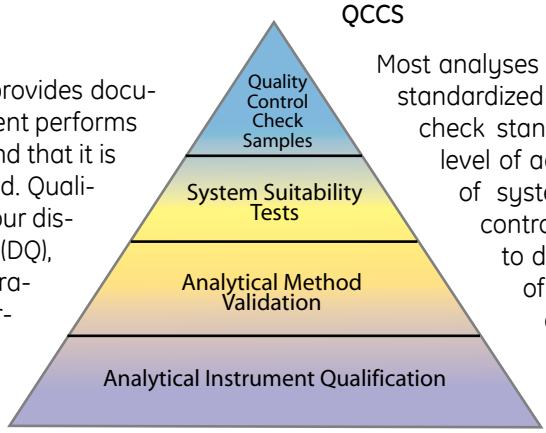
Distinct Components of Analytical Process Validation

There are four critical components involved in generating reliable and consistent data as described in USP <1058>. In order to validate an analytical process, these four components must be addressed. The following figure shows these components as layered activities within a quality triangle and also demonstrates Analytical Instrument Qualification (AIQ) as the founda-

tion of obtaining reliable and consistent data from an analytical instrument. The other components essential for generating quality data are analytical method validation (AMV), system suitability tests (SST), and quality control check samples (QCCS).[4]

AIQ

As described in USP <1058>, AIQ provides documented evidence that the instrument performs suitably for its *intended purpose* and that it is properly maintained and calibrated. Qualification normally is grouped into four distinct phases: design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). USP <1058> provides an in-depth description and characteristics of each qualification step.



Quality Triangle[4]

AMV

As mentioned above, AMV is the documentation that encompasses evidence and data that the analytical methodology or procedure is suitable for its *intended use*. Use of a validated procedure with qualified analytical instruments provides confidence that the procedure will generate test data of acceptable quality.[4]

SST

System Suitability Tests are performed with sample analyses to ensure that the instrument's performance is "acceptable" at the time the instrument is tested. For the TOC method that is used for compendial purposes (Chapter <643>), the acceptance criteria for passing system suitability is a response efficiency between 85% and 115%.

It is also suggested that, if TOC is used as an analytical method for cleaning validation/verification protocols, a USP system suitability test may *not* be adequate to confirm an instrument's performance under actual conditions of use, as the system suitability test may or may not be testing a value equal to or near the cleaning validation acceptance criteria. If the intended purpose of the USP system suitability procedure is mainly used to check the suitability of the instrument for measuring TOC in PW and WFI, not necessarily cleaning validation, then it is recommended to perform a check verification with a check standard at or around the acceptance criteria or residue limit established for the cleaning validation protocol, (e.g. 10 ppm C or 1 ppm C).

QCCS

Most analyses are performed on instruments standardized using reference materials as check standards at or around a certain level of acceptance criteria. The extent of system suitability and/or quality control check sample testing needed to demonstrate a continuing state of control might vary depending on the complexity or difficulty of the analysis, (e.g. cleaning validation samples). It is not uncommon for TOC analyzers that are being used for analytical method analysis or cleaning validation to be tested with one check standard at the beginning of the analysis and one check standard at the end of the test samples. This verification "bracketing" approach is highly acceptable, but should be considered both from a quality/risk standpoint as well as a "practicality" standpoint.

USP <1058> also classifies instruments into three categories (A, B, and C), again based upon their complexity and proposed level of qualification. The conformance of Group A instruments to user requirements is determined by visual observation; no independent qualification process is required. Examples of Group A instruments include spatulas, ovens, magnetic stirrers, microscopes, and vortex mixers. The conformance of Group B instruments to user requirements is determined according to the instruments' SOP, and their failure usually is readily discernable. Examples of instruments that fall into this category are pH meters, balances, thermometers, refrigerator–freezers, and vacuum ovens. Group C instruments are defined as highly method-specific, complex instruments with conformance determined by their application. Full qualification should be applied to instruments in this group. Examples include high performance liquid chromatography (HPLC) and gas chromatography (GC) instruments, spectrometers, mass

spectrometers, and electron microscopes. Again, TOC instruments could fall into either Group B or Group C, depending upon the intended purpose of their use in the application.

Clearing Up Confusion on USP <1058>, <1225> and <1226>

Effective validation begins with a proper statement of the purpose of the method. For both validation and verification, one must remember the underlying purpose of the TOC method, whether it is used for monitoring and approving USP grade water or approving a cleaning process.

If the method is from the pharmacopeia and is intended to be used in demonstrating that a pharmacopeial article meets requirements (for which there is a monograph), the method is considered to be validated, and it would be necessary to verify that the test article is suitable for use with the method, as is the case for using TOC with regard to USP Chapter <643>. If the method is from the pharmacopeia, but is not intended for use in satisfying monograph requirements, it may need to be validated relative to the specific non-pharmacopeial purpose (e.g. analytical method used for cleaning validation) following approved and accepted ICH guidelines. Finally, if the non-pharmacopeial method is not intended to satisfy monograph requirements (USP <643>), it *must* be validated according to its *specific purpose*, and this would not require comparison to any pharmacopeial method or specific analytical method like HPLC <621>.

Conclusion

The extent of qualification required for a TOC instrument is dependent upon the USP <1058> category into which it is placed. This categorization is based on the intended use of the instrument. TOC instruments will typically be classified in either Group B or Group C. If the TOC instrument is merely a monitoring device, providing data for information only, it will most likely be categorized in Group B. If the TOC instrument is providing data to be used in the validation of a process, or the release of a material (such as WFI water release) the instrument must be classified in Group C.

Verification of the particular TOC process to be executed involves testing the instrument's capability to accurately detect a TOC value at or around the value to be tested for in the procedure, and to detect this value under the actual conditions of use. For example, if a particular procedure requires detecting a value of 500 ppb, verification of this procedure will include a testing standard at or around 500 ppb. Testing the instrument "under actual conditions of use" involves placing the instrument in the laboratory, and utilizing the personnel and the procedures that will ultimately be the "conditions" of the instrument.

Validation of a TOC process involves all the requirements of instrument qualification and process verification, *as well as* documented evidence that the instrument and procedure will produce accurate, precise, robust, and repeatable data, even when extremes of the process are tested.

[1] USP PF 32 General Chapter <1226> Verification of Compendial Methods
[2] ISO 9000:2000 clause 3.8.5
[3] ISO 9000:2000 clause 3.8.4
[4] USP PF 32 General Chapter <1058> Analytical Instrument Qualification
[5] M.E. Swartz and I.S. Krull, Analytical Method Development and Validation (Marcel Dekker, New York, 1997)
[6] Pharmacopeial Forum 31(2), 549 (Mar./Apr. 2005)
[7] ICH Q2(R1): Validation of Analytical Procedures: Text and Methodology

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