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Simplifying the Process: Automated USP 643 / EP 2.2.44 Purified Water and Water For Injection Testing Using A Next Generation TOC Analyzer

Application Note

By: Brian Wallace and Stephen Lawson

Background and Objective

The United States Pharmacopoeia (USP) <643> and European Pharmacopoeia (EP) 2.2. 44 monographs provide guidelines and requirements for Total Organic Carbon (TOC) analysis of water for injection and purified water. [1,2] These methods present a system suitability test that compares the recovery of a standard solution (rs) of sucrose, a relatively easy compound to oxidize, and the system suitability solution (rss) of 1,4-benzoquinone, the challenge compound. The response of reagent water (rw) is subtracted from each of these solutions' responses to yield a corrected response (see Equations 1 & 2). The maximum carbon concentration of the reagent water per these monographs is 100 ppb C. However, when reagent water concentrations are below 50 ppb C, greater accuracy may be obtained through lower instrument / reagent blank values. From the results, a response efficiency (E) is calculated by dividing the corrected system suitability solution response by the corrected standard solution response and multiplying by 100 (see Equation 3). According to both pharmacopoeias, the response efficiency must achieve between 85% - 115% for the instrument to be suitable for total organic carbon (TOC) analysis on pharmaceutical pure water (PW) and water for injection (WFI) samples.

$$R1 = rs - rw$$

R1 = corrected standard solution response
rs = standard solution response
rw = reagent water response

Equation 1. Corrected Standard Solution Response (Limit Response)

$$R2 = rss - rw$$

R2 = corrected system suitability solution response
rss = system suitability solution response
rw = reagent water response

Equation 2. Corrected System Suitability Solution Response

$$E = (R2 / R1) * 100$$

E = % response efficiency
R2 = corrected system suitability solution response
R1 = corrected standard solution response

Equation 3. Response Efficiency

If an instrument is to be purchased for analytical testing, then applicability of the instrument to meet compendial requirements must be demonstrated and SOPs must be designed around the instrument for long-term compliance. In the past, sample preparation was a problem for pharmaceutical laboratories in performing the system suitability testing. Standards had to be made using multiple sets of glassware, often by multiple laboratory personnel and each standard was placed into multiple sets of vials. All of these factors contributed to higher levels of background carbon contamination and varying system suitability performance results from analysis to analysis. Using older TOC analyzers, these criteria were more time consuming and difficult to meet. This paper outlines the features of a modern TOC analyzer which improve the longevity of a laboratory's system suitability performance through unattended automated system suitability monitoring,

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Automated Instrument Features to Calibration

Teledyne Tekmar's Fusion TOC analyzer uses Windows Vista®, XP® based software, TekLink™ , that is more powerful and easier to navigate than ever before. TekLink™ has 32 user defined method parameters that allow the end user to customize the instrument for their specific sample needs. The Fusion provides superior analytical analysis for a variety of sample applications. For the USP / EP system suitability test, the Fusion utilizes a default pharmaceutical TOC method that provides the best performance for water-for-injection (WFI), ultra-low purified water. Additionally, this method's robust characteristics are strong enough to handle the most challenging cleaning validation samples. [4-8]

For ease of system suitability analysis, the Fusion analyzer has an integrated autosampler with four center stock solution positions that can hold 125 mL bottles, Figure 1. Unattended multiple runs of the system suitability test reagent water, standard solution, and challenge solution can be analyzed by placing 125 mL bottles in the center positions A, B, C or D of the autosampler. This feature allows the system suitability test to be run at multiple intervals from the center positions; thus, allowing extra available sample positions in the autosampler for sample vials. By utilizing larger sample container to increase system suitability frequency, less risk is incurred of invalid sample results. Further laboratory efficiency and reduction of risk can be achieved by using USP and NIST certified pre-made TOC standards, reagents and purified water. [9, 10] By using scrupulously cleaned TOC 'free' vials, background contributions can be minimized to less than 5ppb from sample containers. [11]

Figure 1. The Fusion uses four Boston round bottles (125mL) in its autosampler's center position for calibration, calibration verification and system suitability analysis.

The software of older TOC analyzers required additional software, such as spreadsheets to complete system suitability calculations. Hence, the process required multiple sets and data transfer to perform compendial analysis. Unlike older software, TekLink™ has automated pass / fail alerts for the system suitability performance. If a result is out of specification set by the end-user, then the software can automatically recalibrate, halt or continue the scheduled analysis (see figure 2 and 3). A typical system suitability analysis autosampler schedule and report for the Fusion TOC Analyzer is shown in Figure 4 and Table 1.

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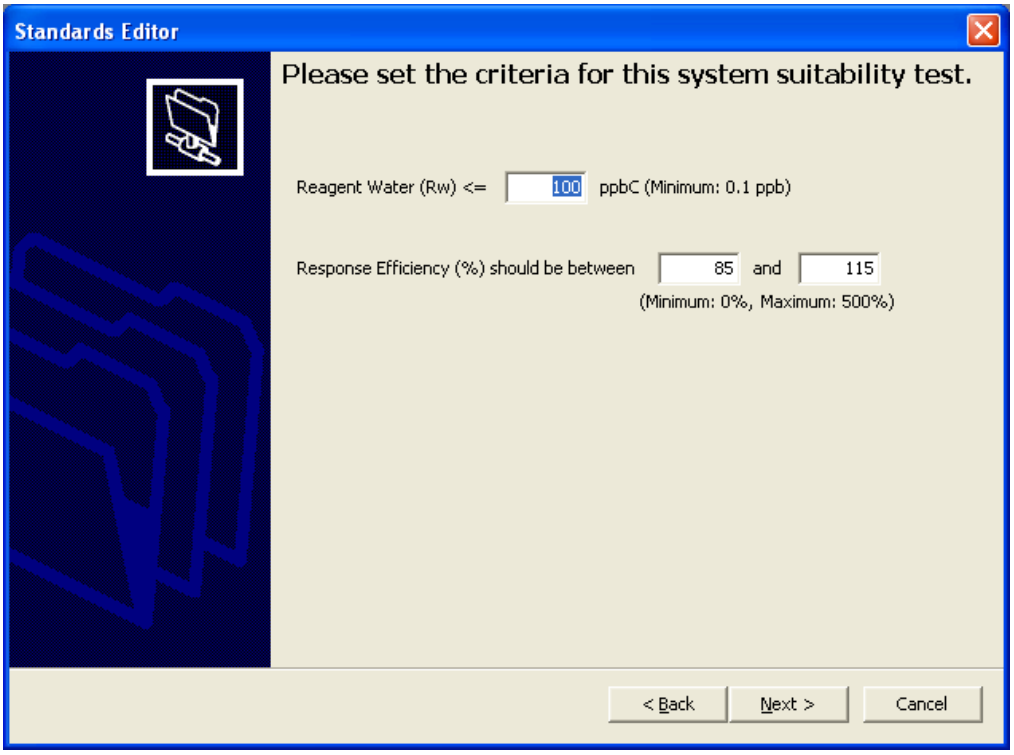

Figure 2 User defined system suitability acceptance criteria

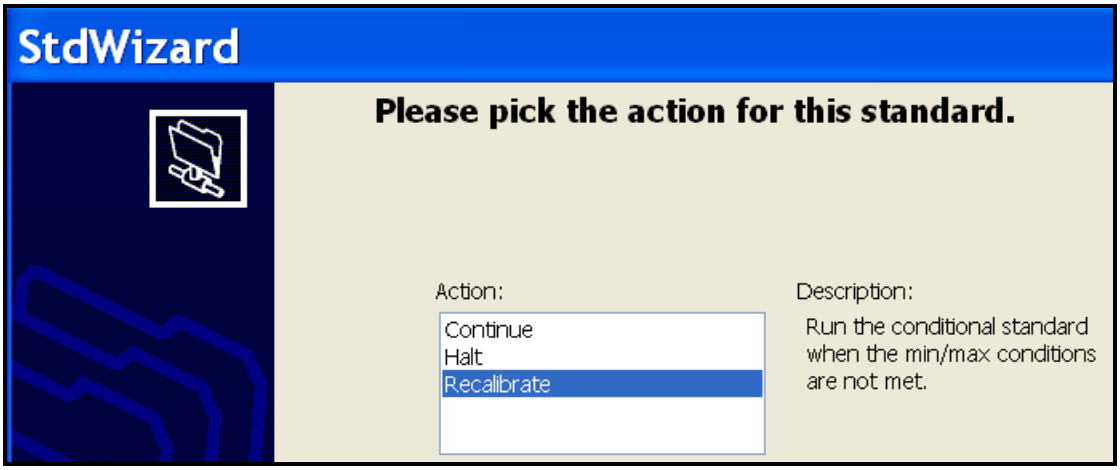

Figure 3. User defined system suitability user-determined actions when acceptance criteria are not met.

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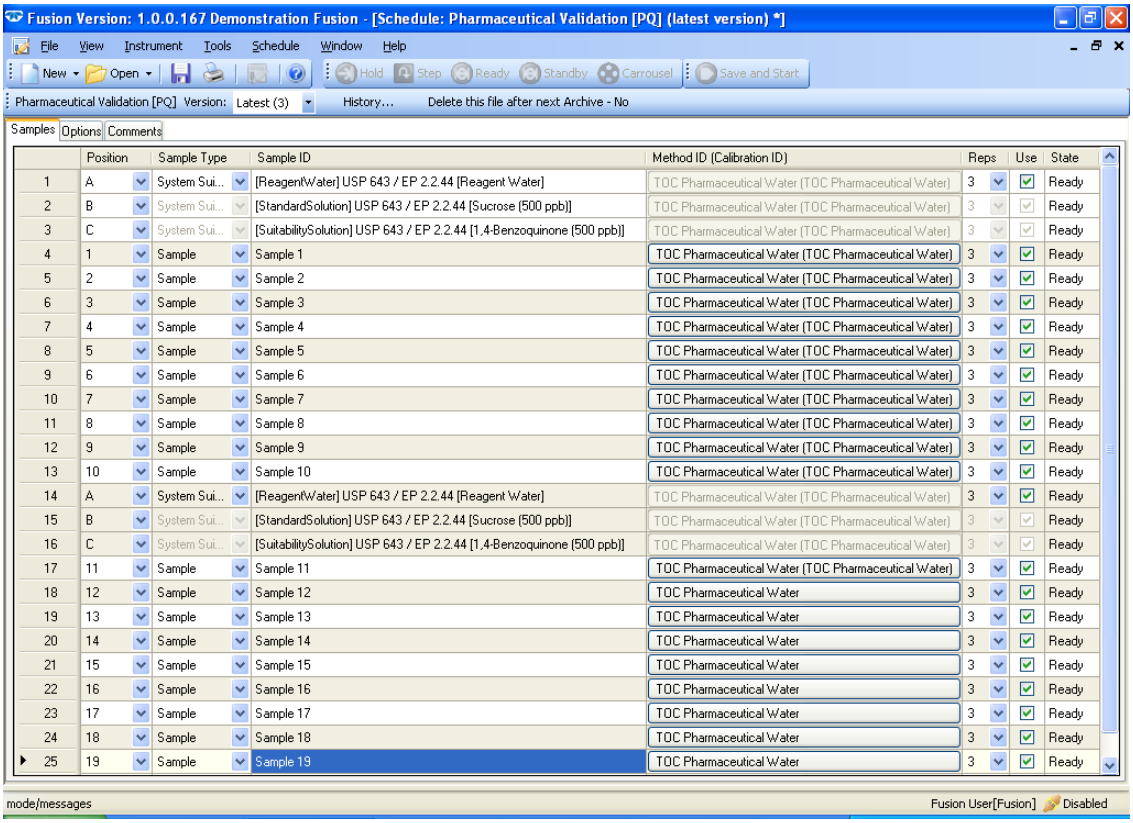

Figure 4 Sample Schedule using system suitability sets to bracket sample analysis within Fusion TekLink™ Software.

Sample Type: System Suitability

Pos	System Suitability Sample Type	Sample ID	Result	Std. Dev.	RSD	Start Time
A	Reagent Water	[Reagent Water] USP 643 / EP 2.2.44	**0.0195 ppm (PASS)**	0.0009 ppm	4.44%	11:59
B	Standard Solution	[Standard Solution] USP 643 / EP 2.2.44 [Sucrose (500 ppb)]	0.4833 ppm	0.0035 ppm	0.73%	12:23
C	Suitability Solution	[Suitability Solution] USP 643 / EP 2.2.44 [1,4-Benzoquinone (500 ppb)]	0.4850 ppm	0.0018 ppm	0.37%	12:46
Response Efficiency: 100.37% (Acceptance Criteria 85% to 115%)		**Limit Response (Ru): 463.8 ppb**				

Table 1. Report from system suitability analysis using Fusion TekLink™ Software are easily exported to HTML, XML or CSV formats for use in documentation and reporting.

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For ease of calibration and calibration verification, the Fusion can utilize a fourth 125mL center stock solution position. My using one stock solution position, multiple calibration points can be attained through auto-dilution using the syringe pumper. This same stock solution can be used to verify the calibration curve through similar auto-dilutions. By utilizing the stock solution for calibrations and verifications, additional sample position can become available for WFI, purified water and cleaning validation analysis. Examples of auto-dilutions of calibration and calibration verification standards sets are shown in figure 5 and 6. Actions when criteria is not met is displayed in figure 7.

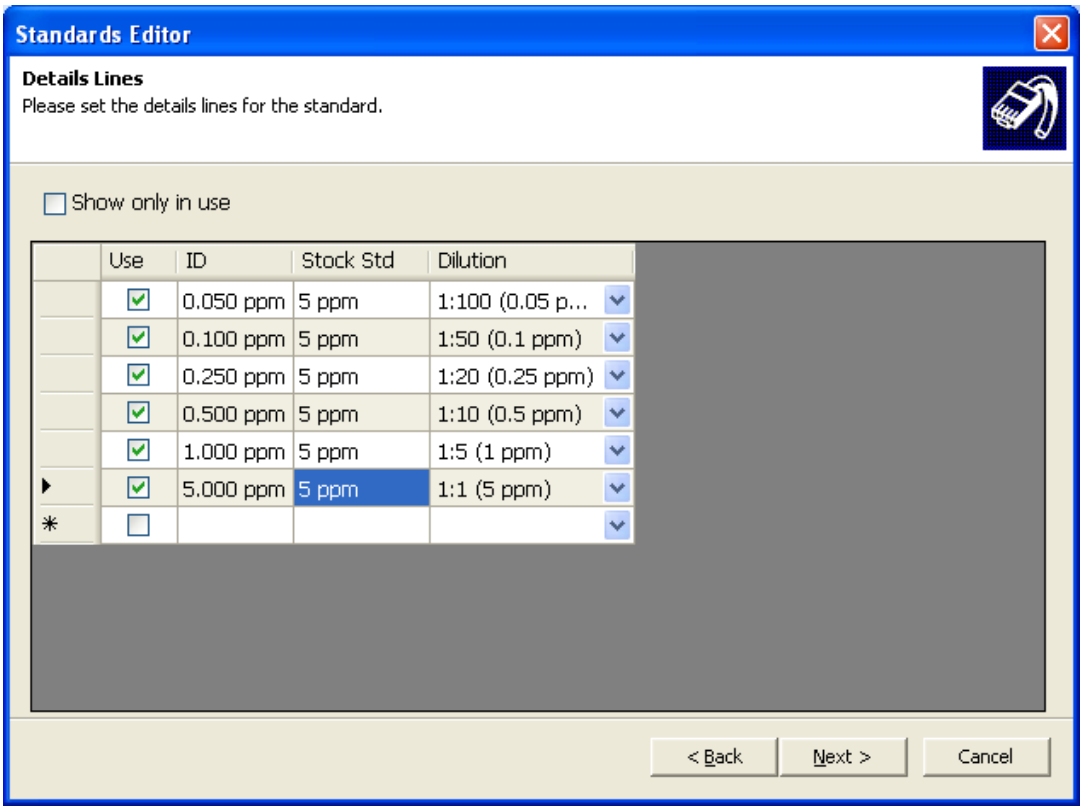

Figure 5 Calibration Curve Standards Set by auto-dilution within the Standards Editor Wizard.

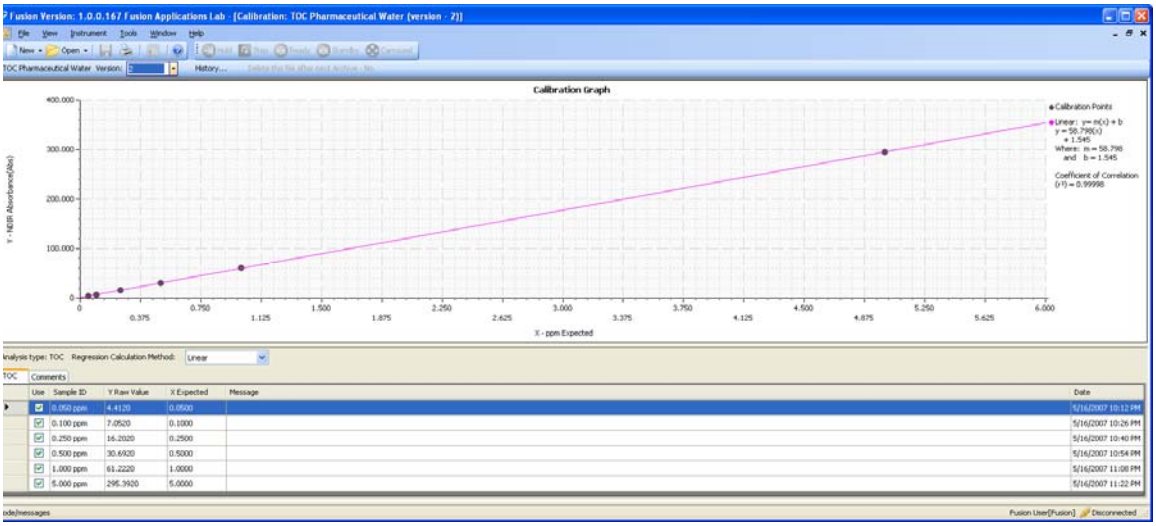

Figure 6 Calibration Curve Example by auto-dilution from a 5 ppm C TOC Stock Solution

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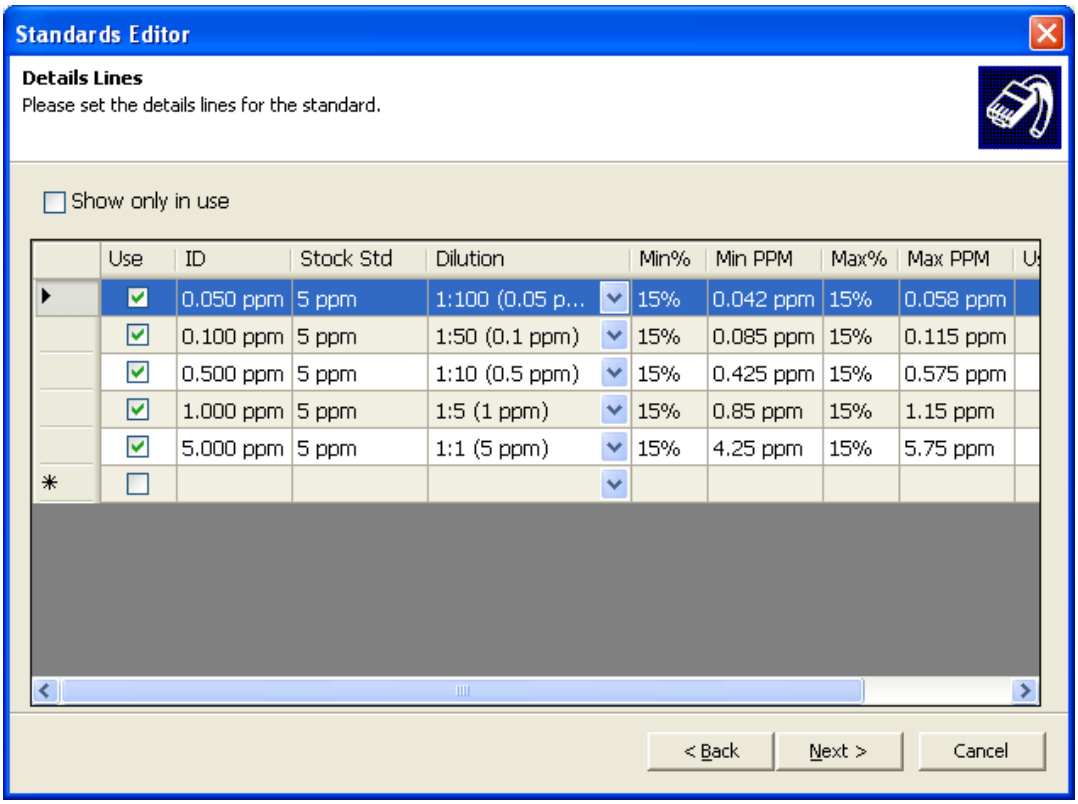

Figure 7 Calibration Verification Set by auto-dilution within the Standards Editor Wizard.

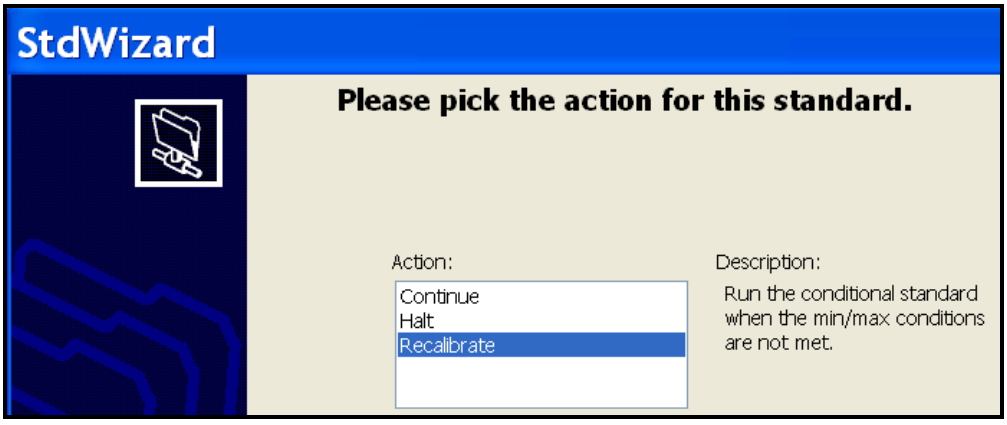

Figure 8. User defined calibration verification user-determined actions when acceptance criteria are not met.

Within the TekLink™ Software, end users can prescribe time saving acceptance criteria. Instrument performance parameters such as R^2 minimum, slope, and Y intercept acceptance criteria can be selected within the options tab of the Standards Editor Wizard (Figure 9). If the calibration does not meet the user-defined criteria, the software can be set to repeat automatically the calibration from a stock position bottle until all the criteria are met (Figure 10). User defined parameters for the calibration check samples can also be set to ensure ideal instrument performance (Figure 7). The acceptance criteria for analysis of samples can be set as well (see Figure 11).

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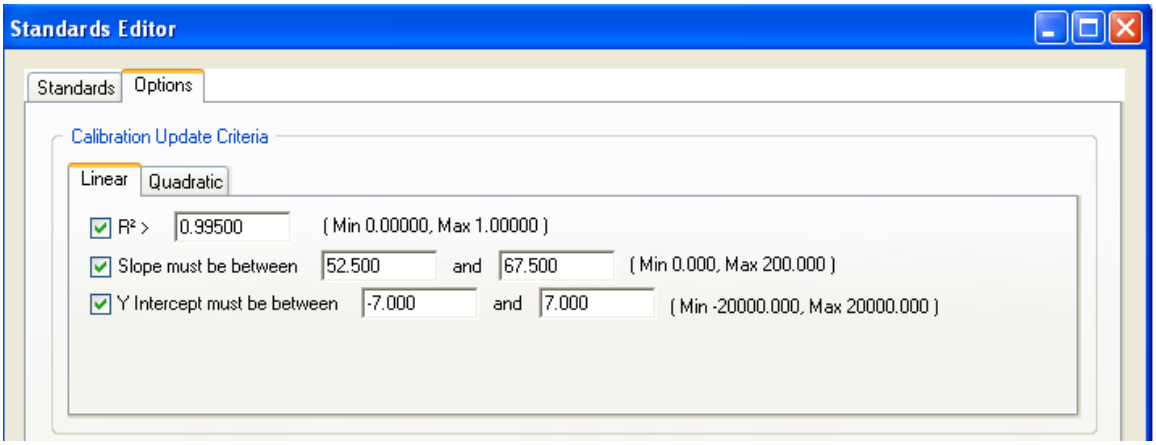

Figure 9. User interface calibration criteria within the Standards Editor Wizard.

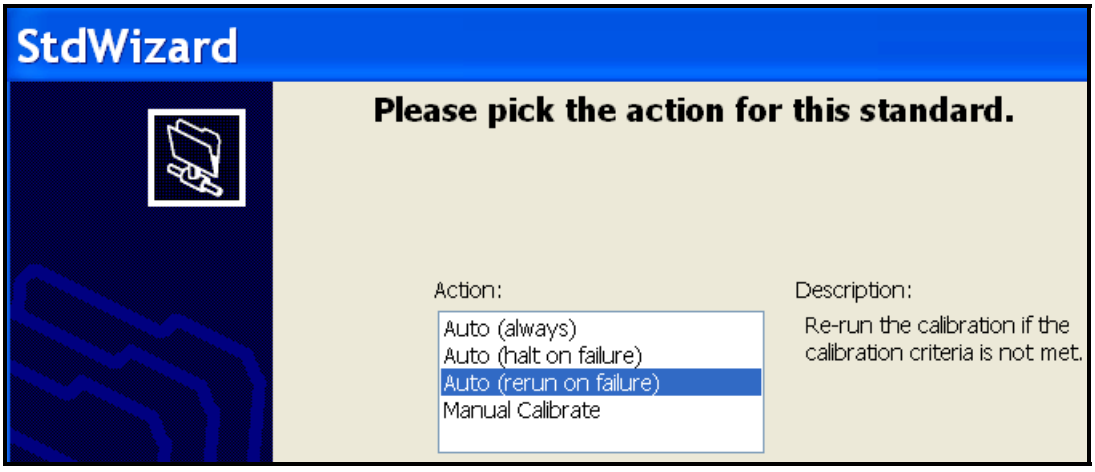

Figure 10. User defined calibration update criteria

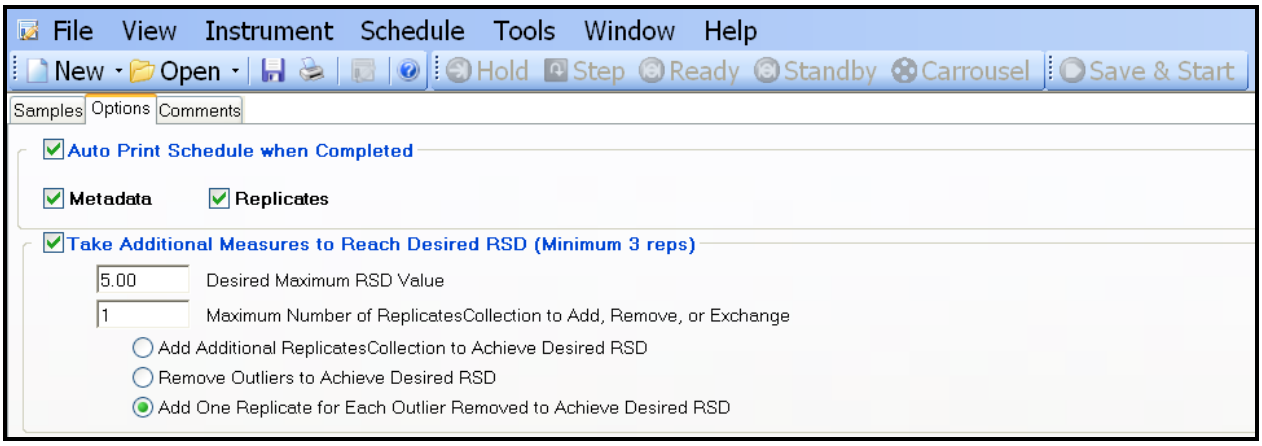

Figure 11. User defined acceptance criteria parameters for sample analysis precision measurements.

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Improving System Suitability Testing and TOC Analysis

Every pharmaceutical laboratory's goal is to operate their TOC analysis with the lowest amount of invalid results. By utilizing the latest technology in automation and reporting, the Fusion TOC analyzer provides unique features that save time and increase laboratory throughput making the task of system suitability performance analysis easier for compliance monitoring. Additionally, successful system suitability result details along with all meta-data (calibration curve, method, electronic signatures and audit trail details) are documented within the sample analysis report.

References

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2. "European Pharmacopoeia Method 2.2.44 – Total Organic Carbon in Water for Pharmaceutical Use/ Carbone organique total dans l'eau pour usage pharmaceutique" European Pharmacopoeia Commission. Implemented 1 July 1999.
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9. Teledyne Tekmar certified, pre-made TOC standards.
10. "Validation Support Package for the Fusion Total Organic Carbon Analyzer and its Accessories." Teledyne Tekmar. Mason, OH. November 2007.
11. Teledyne Tekmar pre-cleaned TOC free vials. *Part Numbers for case of 72 or 144, respectively. 14-7859-000 and 14-7859-100.*

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