Designation: E2656 – 16

Standard Practice for Real-time Release Testing of Pharmaceutical Water for the Total Organic Carbon Attribute[1]

This standard is issued under the fixed designation E2656; the number immediately following the designation indicates the year of original adoption or, in the case of revision, the year of last revision. A number in parentheses indicates the year of last reapproval. A superscript epsilon (ε) indicates an editorial change since the last revision or reapproval.

1. Scope

1.1 This practice establishes an approach to the real-time release testing (RTRT) of pharmaceutical water based on the total organic carbon (TOC) attribute using on-line total organic carbon (OLTOC) instrumentation that is in agreement with current regulatory thinking.

1.2 This practice is harmonized with or supports the concepts of relevant ASTM International Committee E55 on Manufacture of Pharmaceutical Products standards, ICH Harmonized Tripartite Guidelines, the U.S. FDA PAT Guidance, and U.S. FDA Pharmaceutical cGMPs.

1.3 This practice does not provide general guidance information for pharmaceutical procedures that are considered standard practice in the pharmaceutical industry. This practice provides specific guidance for non-standardized procedures.

1.4 This practice does not address the user's various internal procedures for risk, change, or quality management systems. The overall project effort associated with this practice shall be proportional to the overall risk of failing the pharmaceutical water's TOC concentration specification.

1.5 This practice does not purport to establish how to comply with pharmacopeias. The RTRT methodology selected must assure compliance with the user's current required pharmacopeias. However, compliance with pharmacopeia TOC methods is not necessarily sufficient to meet current regulatory expectations for RTRT.

1.6 This practice does not purport to substitute for or replace compendial bioburden testing requirements. It is strictly applicable to the TOC attribute of water quality.

1.7 *This standard does not purport to address all of the safety concerns, if any, associated with its use. It is the responsibility of the user of this standard to establish appropriate safety and health practices and determine the applicability of regulatory limitations prior to use.*

2. Referenced Documents

2.1 *ASTM Standards:*[2]

E2281 Practice for Process Capability and Performance Measurement

E2363 Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry

E2500 Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment

E2537 Guide for Application of Continuous Quality Verification to Pharmaceutical and Biopharmaceutical Manufacturing

D4839 Test Method for Total Carbon and Organic Carbon in Water by Ultraviolet, or Persulfate Oxidation, or Both, and Infrared Detection

D5173 Guide for On-Line Monitoring of Total Organic Carbon in Water by Oxidation and Detection of Resulting Carbon Dioxide

D5904 Test Method for Total Carbon, Inorganic Carbon, and Organic Carbon in Water by Ultraviolet, Persulfate Oxidation, and Membrane Conductivity Detection

D5997 Test Method for On-Line Monitoring of Total Carbon, Inorganic Carbon in Water by Ultraviolet, Persulfate Oxidation, and Membrane Conductivity Detection

D6317 Test Method for Low Level Determination of Total Carbon, Inorganic Carbon and Organic Carbon in Water by Ultraviolet, Persulfate Oxidation, and Membrane Conductivity Detection

2.2 *Pharmacopoeia Documents:*

ICH Q2 (R1) Validation of Analytical Procedures: Text and Methodology[3]

ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients[3]

ICH Q8 (R2) Pharmaceutical Development[3]

[1] This practice is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical and Biopharmaceutical Products and is the direct responsibility of Subcommittee E55.03 on General Pharmaceutical Standards.

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[2] For referenced ASTM standards, visit the ASTM website, www.astm.org, or contact ASTM Customer Service at service@astm.org. For *Annual Book of ASTM Standards* volume information, refer to the standard's Document Summary page on the ASTM website.

[3] Available from International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Secretariat, c/o IFPMA, 15 ch. Louis-Dunant, P.O. Box 195, 1211 Geneva 20, Switzerland, http://www.ich.org.

ICH Q9 Quality Risk Management[3]
ICH Q10 Pharmaceutical Quality System[3]
ISO 15839 Water Quality — On-line Sensors/Analyzing Equipment for Water: Specifications and Performance Tests[4]
JP Chapter <2.59> Test for Total Organic Carbon[5]
Ph. Eur. Chapter <2.2.44> Total Organic Carbon in Water for Pharmaceutical Use[6]
U.S. FDA Part 11 Guidance Guidance for Industry: Part 11, Electronic Records; Electronic Signatures — Scope and Application[7]
U.S. FDA PAT Guidance Guidance for Industry: PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance[7]
U.S. FDA Pharmaceutical cGMPs Pharmaceutical cGMPs for the 21st Century — A Risk-Based Approach[7]
U.S. FDA Procedures and Methods Validation Guidance for Industry: Analytical Procedures and Methods Validation Chemistry, Manufacturing, and Controls Documentation[7]
U.S. FDA Process Validation Guidance Guidance for Industry: Process Validation: General Principles and Practices[7]
USP Chapter <643> Total Organic Carbon (TOC)[8]
USP Chapter <1225> Validation of Compendial Procedures[8]
USP Chapter <1226> Verification of Compendial Procedures[8]
USP Chapter <1231> Water for Pharmaceutical Purposes[8]
USP Guidance <1058> Analytical Instrument Qualification[8]

3. Terminology

3.1 For definitions of terms specific to this standard, refer to the Terminology sections of Practice E2281, Terminology E2363, and Guide E2500. Refer to ICH Q2 (R1) for method validation terminology.

4. Summary of Practice

4.1 This practice provides the user with sufficient guidance for developing the scientific and risk-based information necessary to make informed decisions on the implementation, continuous verification, and continuous improvement of a system to provide the real-time release testing of pharmaceutical water using on-line total organic carbon (RTRT-OLTOC) instrumentation that meets pharmaceutical water TOC specifications. This guidance is based on Practice E2281, Terminology E2363, and Guide E2500 standards as well as ICH Q2 (R1), ICH Q7, ICH Q8 (R1), ICH Q9, and ICH Q10 guidelines. The following steps are required to meet the objectives of this practice.

4.1.1 *Technical Evaluation*—Evaluate and understand water systems, TOC measurement technologies, and the related regulatory requirements.

4.1.2 *Risk Assessment*—Perform quality risk analysis on the prospective RTRT system designs to establish the sampling locations representative of the point-of-use.

4.1.3 *Data Quality*—Ensure the quality of the data from the TOC measurement system is suitable for the intended use in the water RTRT system. Ensure equivalency/consistency to data from existing TOC measurement systems used to release water to the TOC attribute, if they exist.

4.1.4 *Implementation Strategies*—Develop process to assure successful implementation of RTRT.

4.1.5 *Continuous Verification Procedures*—Develop quality control strategies to ensure consistent system performance.

4.1.6 *Continuous Process Improvement*—Assess and implement process improvement practices.

5. Significance and Use

5.1 Pharmaceutical water is the most common component or ingredient used in pharmaceutical and biopharmaceutical manufacturing. Acceptable purity of the water is important to the quality of the final pharmaceutical product. TOC concentration is a key indicator and attribute of the purity of this water and also an important monitor of the overall performance of the water purification system. TOC analysis is the measurement of all the covalently bound carbon present in the water, not including carbon in the form of carbon dioxide (CO_2), bicarbonate icon (HCO_3^-), or carbonate ion (CO_3^{2-}), and is reported as the mass of organic carbon per volume.

5.2 Application of this practice provides pertinent information to make informed decisions on the release of water meeting pharmaceutical TOC concentration specifications.

6. Procedure

6.1 *Technical Evaluation:*

6.1.1 The overall project scope shall be proportional to the associated risk of exceeding the pharmaceutical water TOC concentration specifications. Knowledge and understanding of the TOC concentration in the water system, the OLTOC measurement system technology performance, and the pharmaceutical water system design shall be acquired to minimize risk, ensure correct quality decisions, and maximize return on investment (USP Chapter <1231> and **(1-7)**[9]). TOC measurement technologies are referenced in Test Methods D4839, D5904, D5997, and D6317, and Guide D5173.

6.1.2 Technical assessments should be conducted to evaluate and develop a low-risk, science-based RTRT-OLTOC system design. Knowledge of related information from available sources should be used to understand, interpret, and implement the results of the technical assessments. Information on general and specific RTRT-OLTOC system design considerations, performance characteristics, and validation should be found in published documents and texts **(8-15)**.

[4] Available from International Organization for Standardization (ISO), 1, ch. de la Voie-Creuse, Case postale 56, CH-1211, Geneva 20, Switzerland, http://www.iso.ch.

[5] Available from Japanese Pharmacopoeia (JP), Standards Division, Office of Compliance and Standards, Pharmaceuticals and Medical Devices Agency (PMDA), Shin-kasumigaseki Building, 3-3-2, Kasumigaseki, Chiyoda-ku, Tokyo 100-0013, Japan, http://www.std.pmda.go.jp.

[6] Available from European Pharmacopoeia (Ph. Eur.), 7 allée Kastner, CS 30026, F67081 Strasbourg, France, http://www.pheur.org.

[7] Available from Food and Drug Administration (FDA), 5600 Fishers Ln., Rockville, MD 20857, http://www.fda.gov.

[8] Available from U.S. Pharmacopeia (USP), 12601 Twinbrook Pkwy., Rockville, MD 20852-1790, http://www.usp.org.

[9] The boldface numbers in parentheses refer to a list of references at the end of this standard.

6.1.3 For existing water purification systems, the user should assess historical, current, and potential organic contamination. Evaluation of potential organic contamination should be based on a realistic assessment of water system design and components to determine the probability of a specific or a broad spectrum of organic contaminants reaching the water distribution system. The user should consult with TOC instrumentation vendors to determine if the TOC measurement system will meet the requirements of the intended application in light of any organic contamination assessment.

6.1.4 For new water purification systems, the presence of potential problematic compounds in the pharmaceutical water system shall be addressed during the design and qualification and validation activities and correction/mitigation/preventive actions shall be implemented accordingly.

6.1.5 TOC measurement system technology assessments shall be achieved by meeting regulatory guidance requirements on analytical procedure verifications and validations (ICH Q2 (R1), USP Chapter <1225>, and U.S. FDA Procedures and Methods Validation). The requirements shall depend on the use of the data and the intended use of the instrumentation.

6.1.5.1 *Legal U.S. Requirements and Verification of* USP Chapter <643>—The use of USP Chapter <643> TOC is legally recognized to meet the requirements for testing the TOC attribute in pharmaceutical water. The users of USP Chapter <643> TOC are not required to validate this practice, but they shall verify it is suitable under actual conditions of use. The user shall understand that Section 501(b) of the U.S. Food, Drug, and Cosmetic Act (the Act) legally recognizes the analytical procedures in the U.S. Pharmacopeia/National Formulary (USP/NF) for purposes of determining compliance with this Act (U.S. FDA Procedures and Methods Validation). The U.S. Federal Regulation CFR 211.194(a)(2) states: the suitability of a compendial analytical procedure must be verified under actual conditions of use. Users shall use USP Chapter <1226>, ICH Q2 (R1), or equivalent to verify compendial procedures.

6.1.5.2 The procedure for validation and verification of the TOC analytical method shall depend on the analytical procedure classification in ICH Q2 (R1), USP Chapter <1225>, or the U.S. FDA Procedures and Methods Validation. The measurement of the TOC attribute in water shall be classified as an impurity test. Under impurity tests are two additional classifications, quantitative and limit test. For each of these, there are recommended lists of validation tests to perform. All pharmacopeia TOC test methods are limit tests. Limit testing produces only a *pass* or *fail* output as graphically represented by Fig. 1. To control, trend, and monitor on-line systems and to release water in real time using quantitative data, the analytical method requires the use of quantitative data, so the analytical method shall be validated to the requirements of quantitative tests (U.S. FDA PAT Guidance). Quantitative data use is graphically represented in Fig. 2. Classifications and recommended tests are shown in Table 1. Additional helpful information can be found in ISO 15839.

6.1.5.3 The U.S. FDA considers "real-time release to be comparable to Alternative Analytical Procedures" and the U.S. Regulation CFR 211.165 requires that the accuracy, sensitivity, specificity, and reproducibility of the alternative analytical test methods or procedures used for process control purposes be validated and documented appropriately (U.S. FDA PAT Guidance and U.S. FDA Procedures and Methods Validation).

6.2 *Risk Assessment:*

6.2.1 If the TOC concentration data is to be used in a quantitative way for trending, process control, or process statistical analysis, a statistical assessment of the process performance should be done to estimate the risk of the process failing the specification requirement. This information should be used in the project implementation phase to understand and improve, if necessary, the combined performance of the water

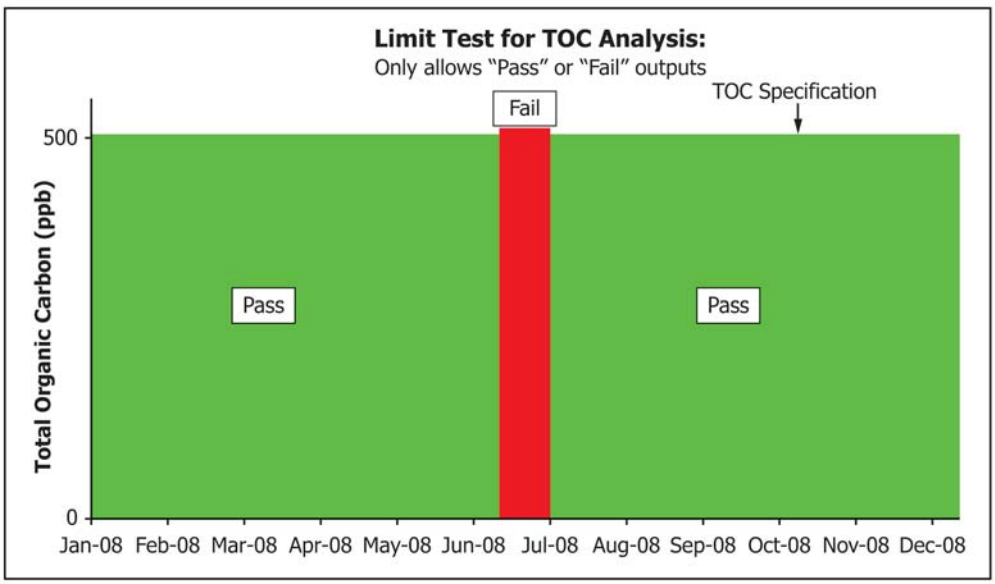

FIG. 1 "Information Poor" Limit Test Output

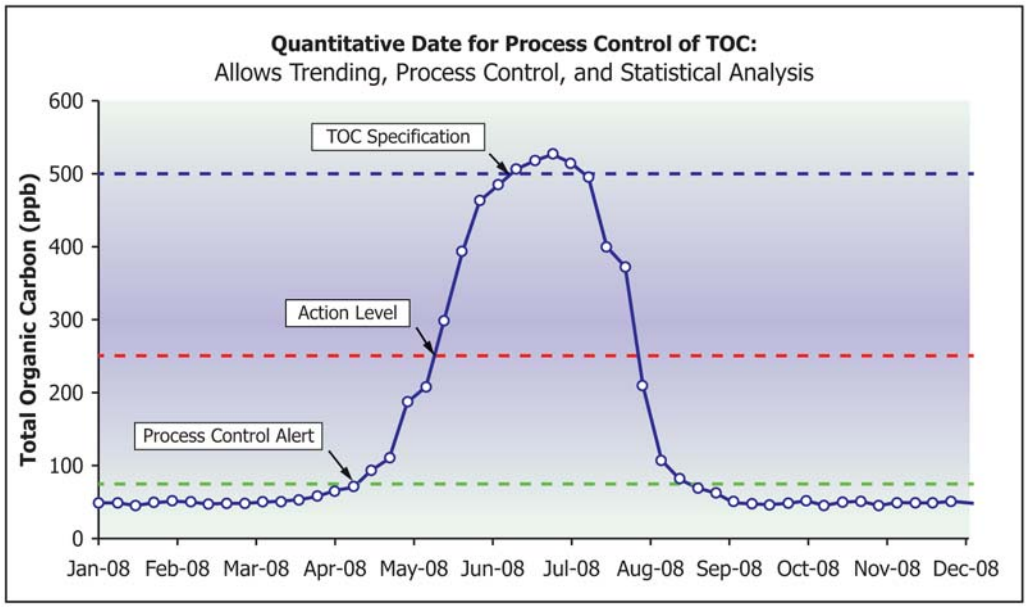

FIG. 2 "Information Rich" Quantitative Data Output

TABLE 1 Verification and Validation Characteristics for Test Procedures

NOTE 1—Table 1 is in accordance with ICH Q2 (R1), USP Chapter <1225>, and U.S. FDA Procedures and Methods Validation.

Type of Validation or Verification Test	Impurity Testing	
	Limit Test (USP Chapter <643>, Ph. Eur. Chapter <2.2.44>, JP Chapter <2.59>, and Other Pharmacopoeias)	**Quantitative** (Trending, Statistical Process Control, C_{pk}, P_{pk}, etc.)
Accuracy	– [A]	+ [B]
Precision	–	+
Linearity	–	+
Range	–	+
Specificity	+	+
Limit of Detection	+	–
Limit of Quantitation	–	+

[A] – signifies that this characteristic is not normal evaluated during method validation or verification.
[B] + signifies that this characteristic is usually evaluated during method validation or verification.

purification system and the TOC measurement system. These statistical assessments should be used for communicating the level of process control for both regulatory inspection and to ascertain the continued performance of the TOC impurity removal and measurement system. See Fig. 3 and Fig. 4 for a graphical presentation of a process with high and low probability of failure.

6.2.2 The placement and connection of the OLTOC instrumentation to the water system should be based on a risk assessment (USP Chapter <643> and (**9**)), as outlined in ICH Q9, or an engineering assessment. The user shall use good engineering design practices and follow cGMP requirements (ISO 15839 and (**1-3, 5, 9, 11**)). The OLTOC measurement location shall represent the quality of the sample as measured at the points-of-use (POU). Water at the POU shall meet the TOC concentration specification. Sample frequency from points-of-use shall be assessed and based on criticality of the water's use. Typical placement of OLTOC instrumentation should be at a connection point in the distribution loop after the POU, before the return to the distribution storage tank, and before any purification processes on the return line. This placement ensures the rapid detection of organic contamination from a point-of-use "reverse flow" condition and should be considered a worst-case location. However, additional OLTOC instrumentation may be placed at other locations as necessary based on risk assessment. For example, instrumentation placed on the output of the water purification system before the feed to the distribution storage tank may be used as a diagnostic and a control tool (if combined with a valve control system) for preventing or limiting the addition of out-of-specification water to the storage tank. In this example, the use of an OLTOC measurement system offers the benefit of additional protection to the storage tank and distribution system by means of earlier TOC impurity detection. The user should consult water system vendors, OLTOC instrumentation suppliers, and other consensus-based published documents for placement recommendations to assure optimum TOC measurement system performance (Guide E2537 and (**3, 5, 9**)).

6.3 *Data Quality:*

6.3.1 To ensure the data from the measurement system is of sufficient quality, the user should follow the guidance of USP Guidance <1058>. The tolerances for the qualification activities should be specified by the instrumentation vendor, but shall be evaluated for their applicability by the user before starting the qualification process.

6.3.2 If the user has historically released water using off-line TOC test methods, the user should "justify how the real time quality assurance is at least equivalent to or better than laboratory based testing on collected samples" in accordance with U.S. FDA PAT Guidance to meet requirements for testing and release for distribution.

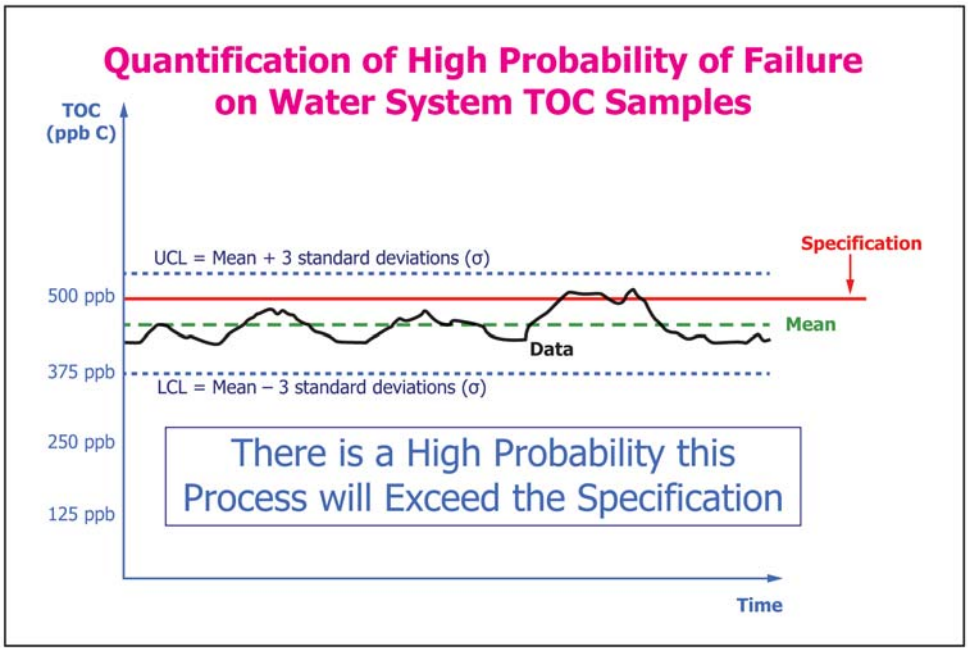

FIG. 3 Diagram of a Process with a High Probability of Failure

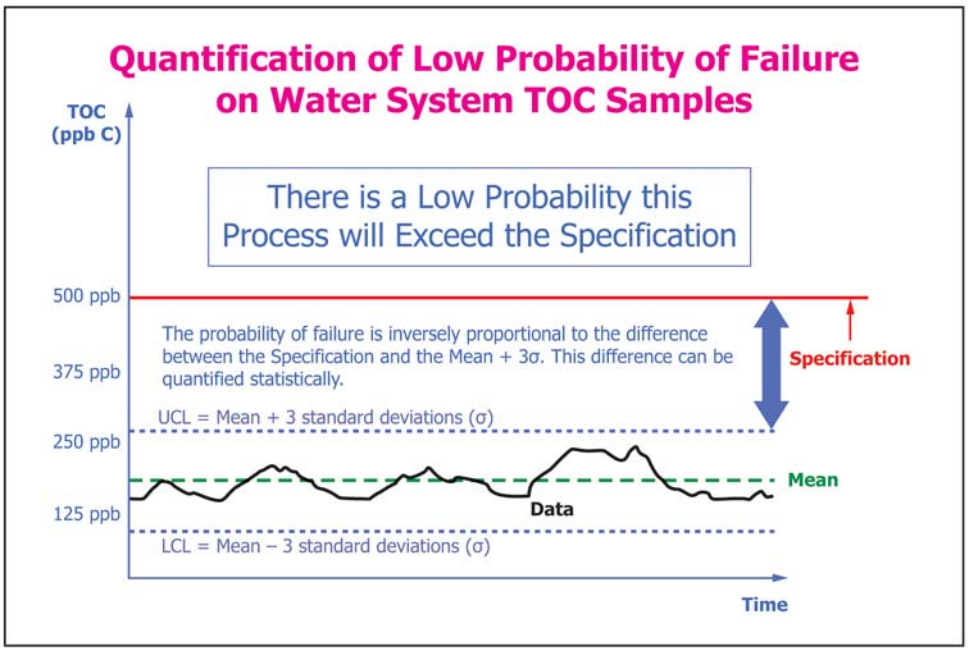

FIG. 4 Diagram of a Process with a Low Probability of Failure

6.3.3 Alternatively, if the user has not historically released water using off-line TOC test methods (for example, a new water system), this practice should allow the user to independently verify the use of on-line equipment to release water meeting the TOC concentration specification.

6.3.4 When operating properly, OLTOC measurements will have lower standard deviation and average values than those of laboratory TOC measurements due to contamination from sample collection and handling. For on-line testing, the water sample is protected by the water system and its piping. Once the sample is exposed to the environment, it is potentially exposed the variables described in Table 2.

6.3.5 If the user of this practice finds it necessary to compare the measurement system performance of OLTOC instrumentation to a laboratory TOC instrument, the comparison should be based on showing that the on-line measurement system capability is equivalent or better than the laboratory measurement system. Since the TOC value includes water system contributions, sampling methods, and TOC measurement system contributions, the water system component can be

TABLE 2 Sources of Contaminations and Variability in TOC Analyses

Off-line TOC Test	On-line TOC Test
Collection of Water Sample Prone to CO_2 and organic contamination from environmental sources like breathing from the person collecting the sample, exposure to organic biological disinfectant agents (alcohol), organics in sample container, and organic fumes in the environment.	Sample Analysis Contamination from reagents (if used) and instrument variability.
Sample Handling and Storage Prone to contamination and TOC sample stability issues.	
Sample Analysis Contamination from labware and reagents (if used), instrument variability, and analyst technique.	

cancelled out by collecting TOC concentration data over the same time period. A statistical assessment of the on-line and off-line results (using common attributes such as average, standard deviation, or C_{pk}) should be used to represent the measurement system variability because the water system component contribution will be the same in both.

6.3.6 The assessment of data quality should include the pharmaceutical water distribution system and the validated points-of-use (POU) like hoses, connections, or production equipment. The data collected should be used to validate the relationship between the validated POU and the data delivered by the OLTOC instrumentation.

6.4 *Implementation Strategies:*

6.4.1 This section describes approaches to RTRT system design, installation, qualification, validation, establishment of alarm levels, and development of standard operational procedures. The user should refer to and follow the recommendations of Guides E2500 and E2537. The user should take care to not overly complicate an otherwise simple system design and verification process. In addition to the recommended guidance, the following points are also useful to consider during implementation:

6.4.1.1 In the event of an out-of-specification TOC measurement condition and to prevent or limit the use of unacceptable water at points-of-use, the user should design an automated sub-system to do one or more of the following: shut off water to the points-of-use, lock out the affected use points, send bad water to drain, flush the use points and the loop, or recirculate the water within the purification system until the TOC value is acceptable.

6.4.1.2 In order to integrate the TOC instrumentation, as a component, into the control system, the user should establish alarm levels, warning levels, a TOC concentration specification limit, and interlocks within the control system (USP Chapter <643>, Ph. Eur. Chapter <2.2.44>, JP Chapter <2.59>, and (**16**)). The user should make provisions to ensure an alarm is not activated when the OLTOC instrumentation is removed from operation for normal service or planned maintenance. The user should make provisions to ensure an alarm condition is activated when the TOC measurement system is not operational for unplanned reasons.

6.4.1.3 The user shall create standard operating procedures (SOPs) for frequency of service, maintenance, calibration, and periodic performance testing of the OLTOC instrumentation and process control equipment, including shut-off or diverter valves. The user shall provide SOPs for suitable actions in the event of a system failure condition, OLTOC instrumentation failure, or water purification system failure including the production of out-of-specification TOC values.

6.4.1.4 The user shall install the OLTOC instrumentation using good engineering practices (GEPs) (Guide E2500 and (**5**)) and in compliance with cGMPs, GLPs, and the manufacturer's recommendations.

6.4.1.5 Using GEPs, the user shall develop automated or manual data collection, security, and archiving systems that provide data for analysis. For data stored in electronic records, these systems should be compliant with the requirements defined in 21 CFR Part 11. At a minimum, each OLTOC value should have associated time and date information. Reasonable preliminary data processing and report generation systems should be developed to detect a TOC impurity problem with the water system, TOC measurement release system, or an out-of-specification condition. Since the TOC instrumentation will produce a considerable volume of data, users should create and validate a report generation system that provides a simple method of demonstrating compliance by exception. Such a report may contain the maximum, minimum, and average for the collection period, plus any alert and action alarm events. This report should be reviewed and approved routinely by the quality team and, along with the raw data, archived for analysis and review.

6.4.1.6 The user should establish acceptable process control levels to prevent the TOC concentration specification from being exceeded. One approach is to establish alert and action levels based on the performance of the process using traditional statistically valid approaches. The user should consider their values with respect to the final TOC concentration specification. Typically, alert levels will be individual to each water system and will provide system information to the operating staff. Typically, action levels will have a greater significance and may signify the need to cease pharmaceutical operations involving the use of the affected water.

6.4.1.7 The user's considerations for TOC measurement frequency should include the following: OLTOC instrumentation delay time, instrumentation response time, TOC instrument measurement cycle time, TOC instrument update rate, maximum expected rate of change of TOC concentrations in water system, rate of water consumption, detection of TOC concentration increases indicative of water system problems, probability of exceeding TOC concentration specification levels, and comparative costs of out-of-specification product. ISO 15839 may provide guidance on useful parameters needed

to set TOC measurement frequency. The user's chosen on-line sampling frequency and TOC measurement frequency should provide confidence that critical water system TOC concentration variations will be detected and properly measured. While the user should assess the importance of on-line measurement frequency in their design, any chosen frequency will be better than the off-line sample testing that can only provide a snapshot in time.

6.5 *Continuous Verification Procedures:*

6.5.1 Continuous quality verification shall require supporting documentation and TOC concentration measurement data to show the process is in a validated state, including a decision on the validated state of this RTRT process. Users should follow the recommendations of Guide E2537.

6.5.2 The user should use process capability and performance indices to assess the combined ability of a pharmaceutical water system and verified TOC measurement system to meet the TOC concentration specification of the water. For impurity measurements of TOC in pharmaceutical water, the user should use the upper process capability (C_{pku}) as the useful process capability index and the upper process performance (P_{pku}) as the useful process performance index. Process acceptability is defined in Practice E2281 and additional information on these indices can be found therein.

6.5.3 The TOC measurement system shall be verified to quantifiably and accurately measure the TOC attribute in the water up to the TOC concentration specification. The user shall take the necessary actions to ensure the process capability or performance index is at least 1.33. When these two actions are true, then the user shall consider the process to be acceptable, in control, and capable of reliably meeting the TOC attribute specification for water quality.

6.5.4 Typical C_{pku} or P_{pku} analysis methods require normally distributed data. If the OLTOC concentration data is not normally distributed due to various reasons such as its proximity to zero TOC concentration (normal distribution truncation) **(17)**, multiple water system operational modes contributing to multiple normal distributions, or other reasons; then the user shall use appropriate non-normal statistical analysis to determine if the process will reliably pass the TOC concentration specification. Such statistical estimation approaches may include the mathematical transformation of the data into a normal distribution, robust non-parametric analysis methods **(18)**, simple comparison of the mean and standard deviations relative to the TOC concentration specification, or other applicable statistical methods.

6.5.5 The user shall create process monitoring, control, analysis, and corrective action plans to provide assurance that the process continues to operate under control.

6.5.6 The user may periodically measure check samples (USP Guidance <1058>) in the OLTOC instrumentation to determine if the calibration or other critical performance characteristics of the instrumentation are nearing or have drifted outside the vendor or user-specified acceptance criteria. Alternatively, the user may support periodic OLTOC instrumentation verification at typical water TOC concentrations, under the actual conditions of use, by using a calibrated on-line reference TOC instrument. In this case, the test and reference instruments shall be setup to measure the water from the same point of use, neighboring point of use, or the exact same water stream using a t-connection for both instruments. A statistical analysis of the data from both instruments shall be performed to verify performance.

6.5.6.1 The OLTOC instrumentation vendor or user should specify the check sample test compound, test concentration, and test frequency. The initial check sample frequency should typically be specified by the TOC instrumentation vendor or the user. The frequency should be changed based on sufficient data that suggests it should be changed and with consideration of the overall risk of failing to meet the TOC concentration specification. The check sample test compound and concentration should be selected based on its ability to detect a deterioration of OLTOC instrumentation performance. Other considerations should include the check sample stability and the determination of the acceptance criteria.

6.5.7 Pharmacopeial system suitability testing for the TOC attribute should be periodically performed (USP Chapter <643>, Ph. Eur. Chapter <2.2.44>, and JP Chapter <2.59>).

6.5.8 An ongoing program to collect and analyze the system data that have potential to impact product quality should be established. This data should be statistically trended and reviewed by trained personnel.

6.5.9 Once the requirements from 6.5.1 – 6.5.8 of this practice have been completed, a decision on "fitness for intended use" shall be made and documented prior to activation of the process (Guides E2500 and E2537), for real-time control.

6.5.10 Once real-time control has been implemented, periodic TOC-RTRT process performance evaluation shall be initiated and should include:

6.5.10.1 The review of OLTOC concentration data against the specification.

6.5.10.2 Periodic or continuous statistical analysis of long-term system upper process capability (P_{pku}) against the acceptance criteria.

6.5.10.3 Evaluation of consolidated process information (including average TOC concentration data and maximum TOC value for a predetermined period) against acceptance criteria.

6.5.10.4 A performance review of any OOSs, alarms, or TOC concentration maximum limit excursions since the last review.

6.5.11 If any process performance criteria have changed and are considered unacceptable, then the user shall perform a root cause analysis. If it makes sense, the user should use this information to improve performance of the water system and to document corrective actions as needed.

6.6 *Continuous Process Improvement:*

6.6.1 The user should meet the guidance on Continuous Process Improvement as found in the U.S. FDA PAT Guidance (Section IV, PAT Framework, Part 1d — Continuous Improvement and Knowledge Management) and Guide E2537 (Section 6.6 — Continuous Process Improvement).

6.6.2 Statistical process capability or performance analysis shall be applied as needed. Except for special causes of process variation (component failures, etc.), the results of this analysis

should be a reliable predictor of the probability of process failure. Based on review of documented process performance, a low risk of exceeding the alarm levels may be used to justify reduced amounts of verification, documentation, or process adjustments.

6.6.3 Effective change control and change management systems shall provide a dependable mechanism for implementing process improvements based on periodic system review and accumulated process performance knowledge.

REFERENCES

(1) Meltzer, T. H., *Pharmaceutical Water Systems*, Tall Oaks Publishing, Inc., Littleton, CO, 1997.

(2) Collentro, W. V., *Pharmaceutical Water — System Design, Operation, and Validation*, Interpharm/CRC, CRC Press LLC, Boca Raton, FL, 1999.

(3) *ISPE Good Practice Guide: Commissioning and Qualification of Pharmaceutical Water and Steam Systems*, International Society for Pharmaceutical Engineering (ISPE), 1st ed., 2007, available online from http://www.ispe.org.

(4) Food and Drug Administration Guidance Document, "FDA Guide to Inspection of High Purity Water Systems," July 1993, available from Food and Drug Administration (FDA), 5600 Fishers Ln., Rockville, MD 20857, http://www.fda.gov.

(5) *ISPE Baseline Pharmaceutical Engineering Guide, Volume 4 — Water and Steam Systems*, International Society for Pharmaceutical Engineering (ISPE), 1st ed., 2001, available online from http://www.ispe.org.

(6) McCurdy, *Implementing TOC Testing for USP 23 — A Case Study*, Pharmaceutical Engineering, Nov/Dec 1997.

(7) Krasner, S., Weinberg, H., Richardson, S., Pastor, S., Chinn, R., Sclimenti, M., Onstad, G., and Thruston, A., "Occurrence of a New Generation of Disinfection Byproducts," *Environmental Science and Technology*, Vol 40, 2006, pp. 7175–7185.

(8) Martinez, J. E., "On-line TOC Analyzers Are Underused PAT Tools," *BioProcess International*, December 2004.

(9) Godec, R., and Cohen, N., "Automated Release of Water Using On-Line TOC Analysis and FDA Risk-Based cGMP, Inspection, and PAT Principles," *Pharmaceutical Engineering*, Jan/Feb 2005.

(10) "Qualification of Analytical Instruments for Use in the Pharmaceutical Industry: A Scientific Approach," *AAPS Pharmaceutical Science and Technology*, Vol 5, No. 1, Article 22, 2004.

(11) Ganguly, J., and Vogel, G., "Process Analytical Technology (PAT) and Scalable Automation for Bioprocess Control and Monitoring — Case Study," *Pharmaceutical Engineering*, Jan/Feb 2006.

(12) Godec, R., "Pharmaceutical Industry Strategies for Releasing Water to Production using Automated On-line TOC Instrumentations," *Ultrapure Water*, March 2005.

(13) "Updating Requirements for Pharmaceutical Grades of Water: Total Organic Carbon," *Pharmacopeial Forum*, Vol 19, No. 4, pp. 5858–5862, and Vol 19, No. 6, p. 6647.

(14) "Monitoring with an Indicator of Total Organic Carbon (TOC)," *Quality Control of Water*, Japanese Pharmacopeia 15, English, General Information, Section 3.5.2, pp. 1740–1741.

(15) Kojima, S., "Lost in Translation with On-line TOC," *Pharmaceutical Manufacturing*, February 2007, p. 9.

(16) "Human Drug cGMP Notes," *U.S. FDA Division of Manufacturing and Product Quality*, Vol 4, No. 4, December 1996, p. 5.

(17) Polansky, A. M., Chou, Y-M., and Mason, R. L., "Estimating Process Capability Indices for a Truncated Normal Distribution," *Quality Engineering*, Vol 11, No. 1, 1999, pp. 257–265.

(18) McCormack Jr., D. W., Harris, I. R., Hurwitz, A. M., and Spagon, P. D., "Capability Indices for Non-normal Data," *Quality Engineering*, Vol 12, No. 4, 2000, pp. 489–495.