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 Manufacturing of Pharmaceutical and Biopharmaceutical Products in the Pharmaceutical and Biopharmaceutical Industry

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

E2537 Guide for Application of Continuous Process 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]

[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 E55.12 on Process Applications.

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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 Q8 (R2) Pharmaceutical Development[3]
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

[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.

considerations, performance characteristics, and validation should be found in published documents and texts (**8-15**).

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

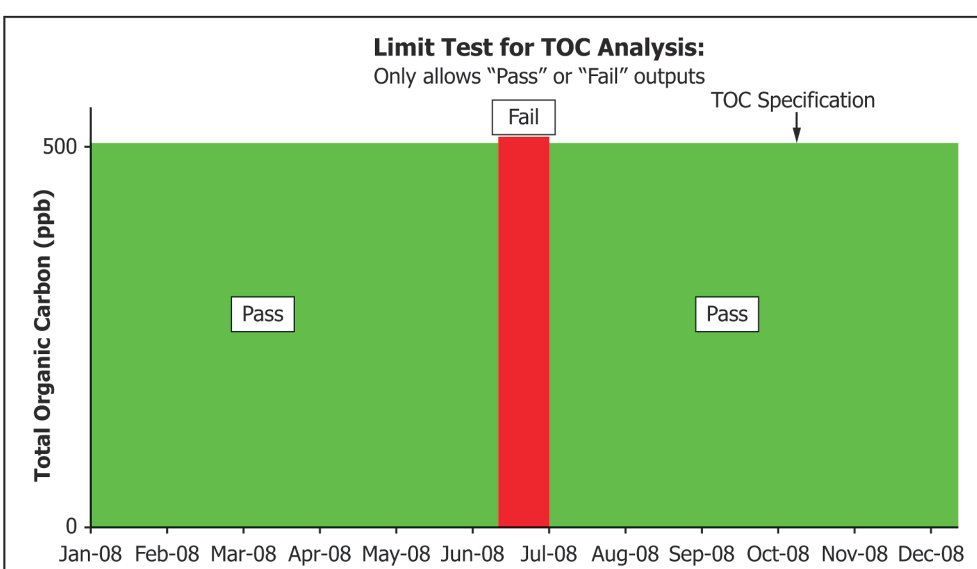

FIG. 1 "Information Poor" Limit Test Output

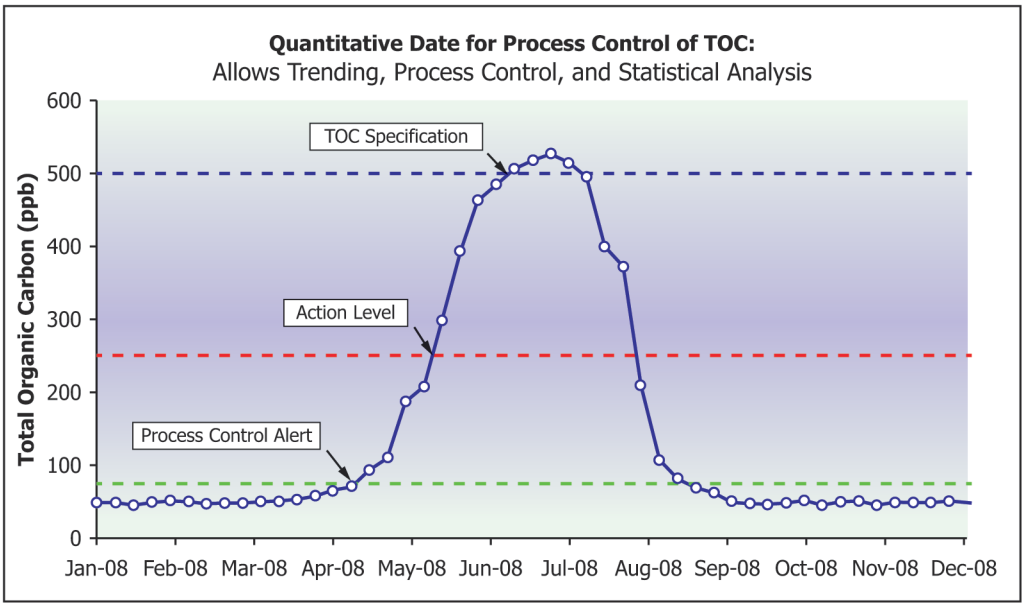

FIG. 2 "Information Rich" Quantitative Data Output

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.