Designation: D 3764 – 01

Standard Practice for Validation of Process Stream Analyzer Systems[1]

This standard is issued under the fixed designation D 3764; 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.

INTRODUCTION

Operation of a process stream analyzer system typically involves four sequential activities. (*1*) **Analyzer Calibration–**When an analyzer is initially installed, or after major maintenance has been performed, diagnostic testing is performed to demonstrate that the analyzer meets the manufacturer's specifications and historical performance standards. These diagnostic tests may require that the analyzer be adjusted so as to provide predetermined output levels for certain reference materials. (*2*) **Correlation–**Once the diagnostic testing is completed, process stream samples are analyzed using both the analyzer system and the corresponding primary test method. A mathematical function is derived that relates the analyzer output to the primary test method (PTM). The application of this mathematical function to an analyzer output produces a predicted PTM result. (*3*) **Initial Validation–**Once the relationship between the analyzer output and primary test method results has been established, an initial validation is performed to demonstrate that the predicted PTM results agree with those from the primary test method within the tolerances established from the correlation activities and with no statistically observable systemic bias. (*4*) **Continual Validation–**During normal operation of the process analyzer system, quality assurance testing is conducted to demonstrate that the agreement between the analyzer and primary test method results during the initial validation is maintained. This practice deals primarily with the third and fourth of these activities.

1. Scope

1.1 This practice describes procedures and recommendations for the validation of a total process analyzer system or its subsystems, or both, used in the direct measurement of physical or chemical characteristics of petroleum and petrochemical products. Procedures for initial validation and subsequent continuous quality assurance of system performance are described.

1.2 Validation is achieved by statistical assessment of results generated for common materials by the total analyzer system or its subsystem versus results generated by an ASTM or other established primary test method (PTM).

1.2.1 For analyzers used in product certification, the analyzer system precision determined by the statistical assessment is typically compared to the site precision for the PTM.

1.2.2 For other analyzer applications, analyzer system precision determined by the statistical assessment is compared to prespecified performance criteria based on the intended use.

1.3 Two procedures for validation are described: the line sample procedure and the validation reference material (VRM) injection procedure.

1.4 Only the analyzer system or subsystem downstream of the VRM injection point or the line sample extraction point is being validated by this practice.

1.5 The line sample procedure is limited to applications where material can be safely withdrawn from the sampling point of the analyzer unit without significantly altering the property of interest.

1.6 Validation information obtained in the application of this practice is applicable only to the type and property range of the materials used to perform the validation.

1.7 Procedures for conducting an initial validation are described. These procedures are typically conducted at installation or after major maintenance once the system mechanical fitness-for-use has been established.

1.8 Procedures for the continual validation of system performance are described. These procedures are typically applied at a frequency commensurate with the criticality of the application.

1.9 This practice applies if the process stream analyzer system and the primary test method are based on the same measurement principle(s), or, if the process stream analyzer

[1] This practice is under the jurisdiction of ASTM Committee D02 on Petroleum Products and Lubricants and is the direct responsibility of Subcommittee D02.25 on Validation of Process Analyzers.

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system uses a direct and well-understood measurement principle that is similar to the measurement principle of the primary test method it is intended to predict.

1.10 This practice is not intended for use if the process stream analyzer system utilizes an indirect or mathematically modeled measurement principle such as chemometric or multivariate analysis techniques. Users should refer to Practice D 6122 for detailed validation procedures for these types of analyzer systems.

1.11 This practice does not address procedures for diagnosing causes of validation failure.

1.12 This practice does not address the methodology for establishing the correlation equation used to generate predicted PTM results using analyzer outputs, nor the expected prediction error. The former is assumed to have been correctly developed as part of the analyzer application development work.

1.13 *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:*

D 1265 Practice for Sampling Liquefied Petroleum (LP) Gases (Manual Method)[2]

D 4057 Practice for Manual Sampling of Petroleum and Petroleum Products[3]

D 4177 Practice for Automatic Sampling of Petroleum and Petroleum Products[3]

D 5842 Practice for Sampling and Handling of Fuels for Volatility Measurements[4]

D 6122 Practice for Validation of Multivariate Process Infrared Spectrophotometers[5]

D 6299 Practice for Applying Statistical Quality Assurance Techniques to Evaluate Analytical Measurement System Performance[5]

E 456 Terminology Relating to Quality and Statistics[6]

F 307 Practice for Sampling Pressurized Gas for Gas Analysis[7]

3. Terminology

3.1 *Definitions:*

3.1.1 *accepted reference value (ARV), n*—a value that serves as an agreed-upon reference for comparison, and which is derived as: (*1*) a theoretical or established value, based on scientific principles, (***2***) an assigned or certified value, based on experimental work of some national or international organization, or (*3*) a consensus or certified value, based on collaborative experimental work under the auspices of a scientific or engineering group.

3.1.2 *precision, n*—the closeness of agreement between independent test results obtained under stipulated conditions. **E 456**

3.1.3 *repeatability conditions, n*—conditions where independent test results are obtained with the same method on identical test items in the same laboratory by the same operator using the same equipment within short intervals of time. **E 456**

3.1.4 *reproducibility conditions, n*— conditions where test results are obtained with the same method on identical test items in different laboratories with different operators using different equipment. **E 456**

3.1.5 *site precision conditions, n*—conditions under which test results are obtained by one or more operators in a single site location practicing the same test method on a single measurement system using test specimens taken at random from the same sample of material, over an extended period of time spanning at least a 15 day interval. **D 6299**

3.1.5.1 *Discussion*—A measurement system may comprise multiple instrument being used for the same test method.

3.1.6 *site precision, n*—2.77 times the standard deviation of results obtained under site precision conditions. **D 6299**

3.2 *Definitions of Terms Specific to This Standard:*

3.2.1 *Analyzer System Items*:

3.2.1.1 *analyzer output, n*—a signal (pneumatic, electrical, or digital), proportional to the property being measured that is suitable for readout or control instrumentation external to the analyzer system.

3.2.1.2 *analyzer system result, n*—the measured property reading, in the accepted property measurement units, that is displayed by the analyzer unit readout instrumentation or transmitted to end user of the analyzer system.

3.2.1.3 *analyzer unit, n*—the instrumental equipment necessary to automatically measure the physical or chemical property of a process or product stream sample using either an intermittent or a continuous technique.

3.2.1.4 *analyzer unit repeatability, n*—2.77 times the standard deviation of results obtained from repetitive analysis of the same material directly injected into the analyzer unit under repeatability conditions.

3.2.1.5 *continuous analyzer unit, n*—an analyzer that measures the property value of a process or product stream on a continuous basis and dynamically displays the instantaneously updated analyzer output.

3.2.1.6 *intermittent analyzer unit, n*—a cyclic type analyzer that performs a measurement sequence on samples from a process or product stream and displays a new analyzer output at the conclusion of each cycle.

3.2.1.7 *total analyzer system, n*—the complete analyzer system inclusive of the sample loop, sample conditioning unit, analyzer unit, readout instrumentation, and excess sample return system (see Fig. 1).

3.2.2 *Time Unit Items—General Terms*:

3.2.2.1 *analyzer unit cycle time, n*—for intermittent analyzers, the time interval between successive updates of the analyzer output.

[2] *Annual Book of ASTM Standards*, Vol 05.01.
[3] *Annual Book of ASTM Standards*, Vol 05.02.
[4] *Annual Book of ASTM Standards*, Vol 05.03.
[5] *Annual Book of ASTM Standards*, Vol 05.04.
[6] *Annual Book of ASTM Standards*, Vol14.02.
[7] *Annual Book of ASTM Standards*, Vol 15.03.

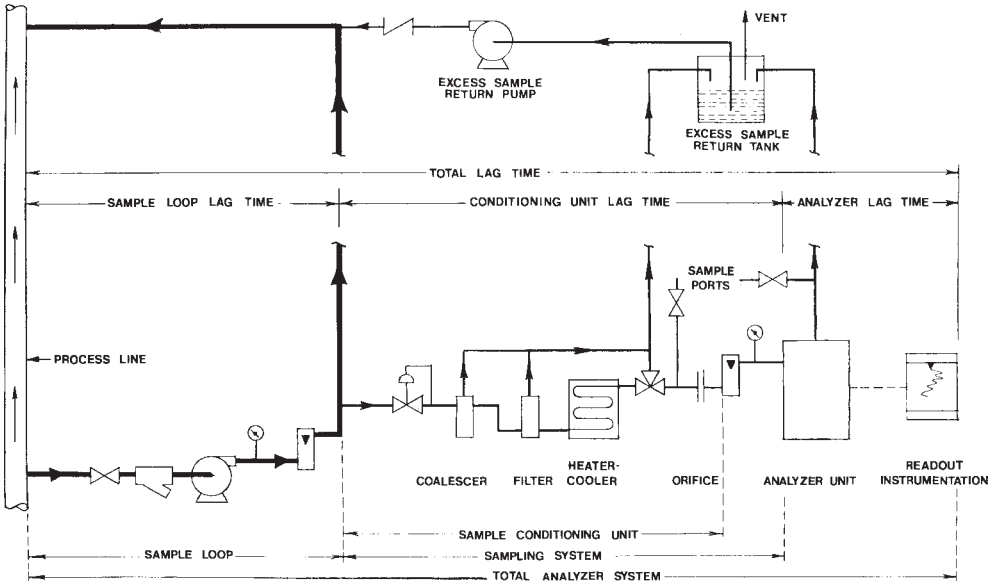

FIG. 1 Total Analyzer System

3.2.2.2 *analyzer unit dead time, n*—the time interval between the introduction of a step change in property characteristic at the inlet of the analyzer unit and the initial indication of analyzer response to this change.

(1) Discussion—For intermittent analyzers, if the analyzer dead time is less than one analyzer unit cycle time, the analyzer unit dead time cannot be directly measured.

3.2.2.3 *analyzer unit response time, n*—(see Fig. 2) the time interval between the introduction of a step change in property characteristic at the inlet of the analyzer unit and when the analyzer output indicates a value corresponding to 99.5 % of the subsequent change in analyzer results;

(1) Discussion—For continuous and intermittent analyzers with sufficiently short cycle times, the total analyzer response time is the analyzer dead time plus three times the analyzer unit time constant. For intermittent analyzers with long cycle times, the analyzer unit response time is effectively equal to the analyzer unit cycle time. For intermittent analyzers with intermediate cycle times, the analyzer unit response time should be defined as the multiple of the analyzer unit cycle time needed to exceed 99.5 % response.

3.2.2.4 *analyzer unit time constant, n*—(see Fig. 2) the time interval between the initial response of the analyzer unit to a step change in property characteristic and when the analyzer output indicates a value corresponding to 63 % of the subsequent change in analyzer results.

(1) Discussion—For intermittent analyzers, if the analyzer unit time constant is less than one analyzer unit cycle time, the analyzer time constant cannot be directly measured.

3.2.2.5 *lag time, n*—the time required for material to travel from Point A to Point B in the total analyzer system (Points A and B are user-defined)

(1) Discussion—Lag time is a function of an analyzer system design parameters such as length and diameter of lines, number of fittings, flow restrictions, and the flow rate of the material (process or product stream) through the analyzer system (see Fig. 1 and Fig. 2).

3.2.2.6 *sample conditioning unit lag time, n*—the time required for material to travel from the start of the sample conditioning unit to the analyzer unit inlet.

3.2.2.7 *sample loop lag time, n*—the time required for material to travel from the process takeoff point of the sample loop to start of the sample conditioning unit.

3.2.2.8 *total analyzer system response time, n*—(see Fig. 2) The time interval between when a step change in property characteristic at the sample loop inlet and when the analyzer

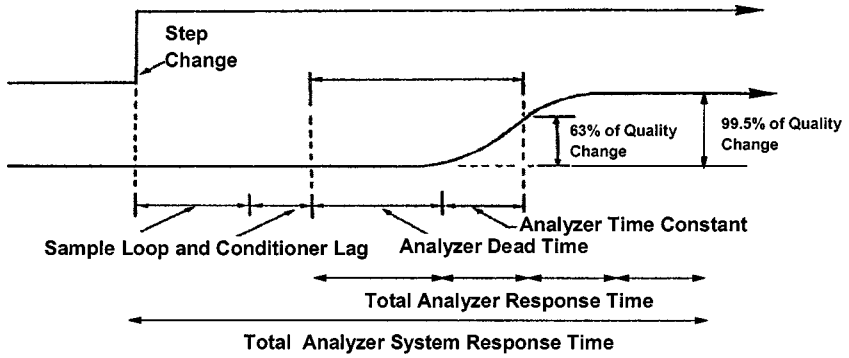

FIG. 2 Analyzer Time Units

output indicates a value *c* corresponding to the 99.5 % of the subsequent change in analyzer results; the total analyzer system response time is the sum of the sample loop lag time, the same conditioning loop lag time, and the total analyzer response time.

3.2.2.9 *composition-specific VRM, n*—a validation reference material consisting of a single, pure compound, or a known, reproducible mixture of compounds for which an accepted reference value or site assigned value can be calculated or measured.

(1) Discussion—A composition-specific VRM may be a commercial standard reference material (SRM) having a certified accepted reference value.

3.2.2.10 *continual validation, n*—the quality assurance process by which the bias and precision performance determined during initial validation are shown to be sustained.

3.2.2.11 *direct measurement, n*—a quantitative measurement result obtained using a principle or principles that express the characteristic property of interest in its defining units.

3.2.2.12 *indirect measurement, n*—a correlated quantitative measurement result obtained using a measurement principle that produces values that do not express the desired characteristic property but which can be modified empirically, using mathematical modeling techniques, to estimate the necessary defining units of the property of interest.

(1) Discussion—Methods that utilize chemometric or multivariate analysis are indirect measurements for generating correlative characteristic property measurement results.

3.2.2.13 *initial validation, n*—validation that is performed when an analyzer system is initially installed or after major maintenance, once system mechanical fitness-for-use has been established.

3.2.2.14 *line sample, n*—process material that can be safely withdrawn from a sample port and associated facilities located anywhere in the total analyzer system without significantly altering the property of interest.

3.2.2.15 *primary test method (PTM), n*—an ASTM or other established standard test method that produces results accepted as the reference measure of a property.

3.2.2.16 *process-derived VRM, n*—a validation reference material derived from an isolated batch of process or product stream material with chemical or physical characteristics, or both, that is suitable for determination of an accepted reference value or site assigned value for the property of interest.

3.2.2.17 *site assigned value (SAV)*—a property value of a reference material that is based on multiple results from either the analyzer unit or a primary test method, obtained under site precision conditions.

3.2.2.18 *validation, n*—the statistically quantified judgment that the analyzer system or subsystem being assessed can produce predicted PTM results with acceptable precision and bias performance when compared to actual results from a primary test method measurement system for common materials.

3.2.2.19 *validation reference material (VRM)*—for validation and quality assurance testing, a material having an accepted reference value or site assigned value for the property of interest.

4. Summary of Practice

4.1 Either line sample or VRM results from the total analyzer system or its subsystem, and corresponding PTM results for the same materials are obtained. Differences between the analyzer system predicted PTM results and actual PTM results are statistically assessed. Precision and bias statistics are generated and assessed against pre-specified performance criteria. The system or subsystem performance is considered to be validated for materials and property ranges representative of those used in the validation if the performance criteria are met.

4.2 After initial validation, continued statistical quality control analyses are conducted to ensure on-going performance of the analyzer system meets the levels established from the initial validation.

5. Significance and Use

5.1 This practice can be used to quantify the performance of a process stream analyzer system or its subsystem in terms of precision and bias relative to those of a primary test method for the property of interest.

5.2 This practice provides developers or manufacturers of process stream analyzer systems with useful procedures for evaluating the capability of newly designed systems for industrial applications that require reliable prediction of measurements of a specific property by a primary test method of a flowing component or product.

5.3 This practice provides purchasers of process stream analyzer systems with some reliable options for specifying acceptance test requirements for process stream analyzer systems at the time of commissioning to ensure the system is capable of making the desired property measurement with the appropriate precision or bias specifications, or both.

5.4 This practice provides the user of a process stream analyzer system with useful information for on-going quality assurance testing designed to update or revalidate an analyzer system through the application of statistical quality control techniques.

5.5 Validation information obtained in the application of this practice is applicable only to the material type and property range of the materials used to perform the validation. Selection of the property levels and the compositional characteristics of the samples must be suitable for the application of the analyzer system. This practice allows the user to write a comprehensive validation statement for the analyzer system including specific limits for the validated range of application. Users are cautioned against extrapolation of validation results beyond the material type and property range used to obtain these results. (**Warning**—Users are cautioned that for measurement systems that show matrix dependencies, bias information determined from pure compounds or simple mixtures of pure compounds may not be representative of that achieved on actual process or product samples.)

6. System Components

6.1 Fig. 1 illustrates a total analyzer system incorporating a selection and arrangement of components that are typical but not specific for any particular analyzer system. A total analyzer

system design addresses the chemical and physical properties of the process or product stream to be measured, provides a representative sample, and handles it without adversely affecting the value of the specific property of interest. Included are a sample loop, piping, hardware, a sampling port, sample conditioning devices, an analyzer unit instrumentation, any data analysis computer hardware and software, and a readout display.

6.2 *Sample Loop*—Piping connected to the main process stream to deliver a portion of the stream to a location close to the analyzer system with minimum lag time and return the unused material to the main process stream.

6.3 *Sampling System*—Sample probes, valves, lines, containers, pressure regulator, and gages that constitute the equipment employed to obtain a proper sample from the sample loop and introduce either it or a validation standard sample to the analyzer.

6.4 *Sample Conditioning Unit*—A collection of devices to properly treat a portion of the sample from the sample loop so that it meets the requirements for testing by the process analyzer. These components can incorporate temperature or pressure adjustment, change of state (liquid, vapor), or removal of contaminants.

6.5 *Inlet Port*—Appropriate piping with selector valve(s) for placement either at the inlet to the analyzer unit or, when dictated by the measurement specifications, at the inlet to the sample conditioning unit. The purpose of this inlet port is to allow injection of validation standards or other calibration material into the analyzer system with quick switching between these typically containerized materials and the flowing process stream.

6.5.1 For many analyzer systems the inlet port requires a manifold arrangement for validation or quality assurance studies. Such a manifold, with suitable valving, provides a means to use a containerized supply of standby material when a flowing process stream is not available for the purpose. It also permits quick switching between different validation standards when that is desirable.

6.6 *Sample Port*—An appropriate probe or fitting in the piping to permit collection of representative samples for laboratory analyses using a primary test method.

6.7 *Analyzer Unit*—Instrumentation designed to automatically measure the chemical or physical property of a process or product stream sample and provide either an intermittent or a continuous output signal representing the measurement result.

6.8 *Readout Instrumentation*—If it is not an integral component of the analyzer system, a device to display or record or both, the property measurement analyzer result.

7. Preparation of Analyzer System for Validation

7.1 Implementation of this practice requires that the process stream analyzer system operates under conditions specified:

7.1.1 Meets all applicable electrical and safety codes.

7.1.2 Meets the supplier's recommendation.

7.1.3 Complies with operating conditions specified by the manufacturer.

7.1.4 Includes a predicted PTM algorithm, if necessary.

7.2 After installation or major maintenance, conduct such diagnostic tests as recommended by the manufacturer to demonstrate that the analyzer meets the manufacturer's specifications or historical performance levels, or both. If necessary, adjust the analyzer system components so as to obtain recommended analyzer output levels for specified reference materials.

7.3 Inspect the entire analyzer system to ensure it is installed properly, is in operating condition, and is properly adjusted after completion of the initial commissioning procedures.

8. Validation Procedure

8.1 The objective of the validation procedures is to quantify the performance of a process stream analyzer system or its subsystem in terms of precision and bias relative to the precision and bias of the primary test method for the property of interest. The user must specify acceptable precision and bias performance criteria before initiating the validation. These criteria will be dependent on the intended use of the analyzer.

8.1.1 For analyzer systems used in product certification, analyzer system precision criteria will typically be based directly to the site precision of the PTM. Bias criteria will be based on regulatory or contractual requirements.

8.1.2 For analyzer systems used in other types of service, precision and bias criteria must be developed based on the intended use of the analyzer results.

8.2 The line sample procedure directly fulfills the validation objective since the validation results for both the process system and the primary test method are obtained on process samples. Depending on circumstances that are described as follows, the validation reference material procedure may or may not fulfill this objective adequately, particularly when the validation reference materials are composition-specific, or not representative of current process samples.

8.2.1 If the process analyzer system is not based on identically the same measurement principle as the primary test method, or if the sample analyzed by the process analyzer system is not identical to that submitted to the primary test method for analysis (after sample conditioning for both methods are considered), then it is recommended that the line sample procedure be used to validate the process stream analyzer performance.

8.2.2 If the process analyzer system is based on identically the same measurement principle as the primary test method, if the sample analyzed by the process analyzer system (post sample conditioning) is compositionally identical to the material in the process, and, if sample conditioning steps in the PTM do not materially change the sample that was taken from the process and submitted for analysis, then the validation reference material procedure is expected to adequately fulfill the validation objective regardless of the nature of the VRM.

8.2.3 If the process analyzer system is not based on identically the same measurement principle as the primary test method, or if the sample analyzed by the process analyzer system is not identical to that submitted to the primary test method for analysis and the user wishes to use the VRM procedure, then it is recommended that the user conduct validation using both the line sample procedure and the VRM

procedure for a period of time sufficient to demonstrate that the VRM procedure adequately reflects process analyzer system performance.

8.2.3.1 The initial process analyzer system validation should be done using both procedures to demonstrate that both procedures agree on the accuracy of the analyzer predicted PTM results.

8.2.3.2 The statistical quality control for continual validation should be done using both procedures for a period of time adequate to demonstrate that both procedures provide acceptable agreement on the precision and bias of the predicted PTM results.

NOTE 1—If the process analyzer system is not based on identically the same measurement principle as the primary test method, then the analyzer system may react differently to variations in the sample matrix than does the primary test method. In such case, analyzer results for process samples might be biased relative to primary test method results even when the VRM procedure results shown no such bias. The bias can be minimized by using a process stream (test) sample for which an ARV or SAV was determined as the VRM. The test sample used in this fashion should be representative of the current process stream.

NOTE 2—If, due to differences in sample pretreatment, the sample analyzed by the process stream analyzer and the sample analyzed by the primary test method are not identically the same, then the use of the VRM procedure may not accurately reflect agreement between the process analyzer and the primary test method. The VRM may not be affected in the same manner as process samples by the different sample pretreatments. Again, this effect can be minimized by using current process stream (test) samples as VRMs.

8.3 *Line Sample Procedure*:

8.3.1 *General*—This procedure is applicable for analyzer systems that are equipped with sample ports anywhere within the system that can facilitate the safe collection of material intended for analysis by the analyzer unit without significantly altering the property of interest. The subsystem downstream of the sample port is considered to be validated for current process stream samples if validation results are in statistical control, and the predicted PTM results are in agreement with actual PTM results within satisfactory precision and bias limits.

8.3.2 *Line Sample Procedure Requirements:*

8.3.2.1 Select point of line sample withdrawal.

8.3.2.2 Determine the total lag time of the system or subsystem downstream of the sample withdrawal point (see Figs. 1 and 2 for guidance).

8.3.3 *Initial Validation*—Collect analyzer unit results from at least 15 implementations of the line sample procedure under site precision conditions, with nominally 8 to 12 h between each implementation, as follows:

8.3.3.1 Observe the analyzer unit output until the change between readings over at least three subsystem lag times does not exceed the known repeatability of the analyzer unit (that is, the manufacturing process is at steady state). If steady state conditions cannot be achieved, the line sample validation procedure should not be executed at this time. If the analyzer system repeatability is unknown, the repeatability of the primary test method can be used as the reference for data comparison.

8.3.3.2 After steady state has been verified, begin collecting the process line sample from the sample port. Refer to Practices D 1265, D 4057, D 4177, D 5842, or F 307 for procedures for sample collection. Record the time, t_s, corresponding to the start of sample collection. Record the analyzer system result $A_0(t_s)$ observed at t_s. Collect the volume of sample required for PTM analysis. Record the time, t_e, when sample collection ends.

8.3.3.3 If the sample collection interval $t_e - t_s$ is less than the total subsystem lag time, record the analyzer result $A_1(t_s)$ at a time one subsystem lag time interval after t_s. If $A_1(t_s)$ and $A_0(t_s)$ agree to within known analyzer system repeatability, assign $A_1(t_s)$ as the predicted PTM result (A) for the collected line sample. Otherwise, the line sample and results are discarded. Wait until steady state is re-established before beginning the line sample procedure again.

8.3.3.4 If the sample collection interval $t_e - t_s$ is longer than the subsystem lag time, then record analyzer results $A_1(t_s)$ and $A_1(t_e)$ at times corresponding to one total analyzer response interval after t_s and t_e respectively. If $A_1(t_s)$ and $A_1(t_e)$ agree to within the known repeatability of the analyzer system, assign either $A_1(t_s)$ or $A_1(t_e)$, or the average of these two results, as the predicted PTM value (A) for the collected line sample. Otherwise, the line sample and results are discarded. Wait until steady state is re-established before beginning the line sample procedure again.

8.3.3.5 Obtain a PTM result (P) for the line sample collected.

8.3.3.6 For each line sample collected, calculate the difference (Δ) between the analyzer system predicted PTM value (A) and the actual PTM value.

8.3.3.7 Follow the instructions in Practice D 6299 (section on Procedure for Pretreatment, Assessment, and Interpretation of Test Results) and assess all the Δ results following the quality control (QC) sample results protocol. Interpret the control chart generated and determine if the system that generated these Δ results is in statistical control.

NOTE 3—The system that generated the Δ results comprises the analyzer subsystem being validated, the PTM, and the process of obtaining the line samples.

8.3.3.8 If the system that generated the Δ results is in statistical control, proceed with calculation of system precision and bias statistics. Otherwise, investigate the out-of-control points and take appropriate corrective actions to address the root cause(s). Replace the out-of-control points by repeating the line sampling procedure.

8.3.3.9 Assess the standard deviation of the Δ results against the appropriate site standard deviation of the PTM (site precision standard deviation). For certification applications, the standard deviation of the Δ results is typically expected to meet or better 1.4 times the site standard deviation of the PTM. For other applications, the standard deviation of the Δ should meet the specifications for the intended use.

8.3.3.10 Assess the bias by performing a one-sample *t*-test using all the Δ results in accordance with Practice D 6299. If the bias is statistically significant, assess the bias magnitude against the application requirement for practical significance.

8.3.3.11 If both the precision and bias meet the application requirements, the subsystem is considered to have met the

initial validation requirements for materials representative of the line samples used in the assessment.

8.3.3.12 Prepare a validation statement and control charts for the Δ results. Establish control limits based on the results from initial validation.

8.3.3.13 *Continual Validation*—Deploy the control chart constructed for the Δ results into operation. Continue to validate the information from the initial validation by populating the control chart with new Δ results at a frequency commensurate with the criticality of the analyzer application. A recommended frequency is at least once a week. Frequency can be reduced if the subsystem stability and precision is monitored by way of other QC material in accordance with Practice D 6299.

8.4 *VRM Injection Procedure*:

8.4.1 *General*—This procedure requires analyzer system to be equipped with storage and injection facilities designed for the delivery of a VRM into the analyzer unit. The subsystem downstream of the VRM injection point is considered to be validated if validation results are in statistical control, and the predicted PTM results are in agreement with actual PTM results within satisfactory precision and bias limits. The validation applies only for analyses of materials of the same type as the VRM.

8.4.2 Injection procedure requirements.

8.4.2.1 Select the point of injection.

8.4.2.2 Determine the total lag time of the subsystem downstream of the injection point (use Fig. 1 for guidance).

8.4.3 *Initial Validation*—Collect analyzer unit results from at least 15 implementations of the VRM injection procedure for each selected VRM under site precision conditions, with nominally 8 to 12 h between each implementation, as follows:

8.4.3.1 Isolate the subsystem to be validated from the regular process stream sample flow.

8.4.3.2 Commence injection of the VRM.

8.4.3.3 Observe the analyzer unit output until the change between readings over at least three subsystem lag times does not exceed the known repeatability of the analyzer unit (that is, steady state has been reached). If the analyzer system repeatability is unknown, the repeatability of the primary test method can be used as the reference for data comparison.

8.4.3.4 Record the steady state analyzer unit output as the result for one implementation of VRM injection procedure.

8.4.3.5 Pre-treat and assess the collected data in accordance with Practice D 6299, including the construction of the I/MR control charts, using the protocol for a single check standard. Use the SAV instead of the ARV for VRMs that do not have ARVs.

8.4.3.6 If the data exhibits in statistical control behavior, follow the procedure in Practice D 6299 to estimate the site precision and bias of the analyzer subsystem for the specific VRM. For the bias test use the protocol for a single check standard.

8.4.3.7 Assess the standard deviation of results for each VRM against the appropriate site standard deviation of the PTM. For product certification applications, the subsystem is expected to meet or better the site precision of the PTM. For other applications, the standard deviation of the results should exceed the pre-specified precision criteria for the intended use.

8.4.3.8 If the one-sample *t*-test for bias is statistically significant, assess the bias magnitude against the application requirement for practical significance.

8.4.3.9 If both the precision and bias meet the application requirements, the subsystem is considered to have met the initial validation requirements for materials of the same type and property range as the VRMs used in the assessment.

8.4.3.10 Prepare a validation statement and control charts for each VRM. Establish control limits based on results from initial validation.

8.4.4 *Continual Validation*—Deploy the control charts constructed for each VRM. Obtain additional results using the VRM injection procedure at a frequency commensurate with the criticality of the analyzer application (typically at least once a week). Plot results on control charts. Assess control chart status in accordance with procedures in Practice D 6299. The frequency of VRM injection can be reduced if the subsystem stability and precision is monitored by way of other QC material in accordance with Practice D 6299.

8.5 *Validation of Total Process Analyzer System*:

8.5.1 The complete analyzer system, inclusive of the sample loop, can be validated by a combination of line sample and VRM procedure where:

8.5.1.1 The Line sample procedure is deployed to validate the entire system using current production material by sampling from a location located in close proximity to the process takeoff point of the sample loop.

8.5.1.2 The VRM procedure is deployed to validate the analyzer unit for material that is not currently available from the process.

ANNEX

(Mandatory Information)

A1. PROCEDURE FOR DEVELOPING A VALIDATION REFERENCE MATERIAL

A1.1 Determine the number of validation standards and the quantity of each that is appropriate for the proposed validation and quality assurance testing uses for the specific analyzer system application.

A1.1.1 If the analyzer system is known or suspected to produce nonlinear results, at least three validation standards having different accepted reference values can be required.

A1.1.2 The desired quantity of each validation standard shall be sufficient to sustain necessary analyzer system operation long enough to determine the data for initial validation of the system. In addition, it is recommended that enough material be included in a given lot, to permit on-going statistical quality control (SQC) testing after the validated system is placed in service. The quantity of validation standard selected for such SQC testing will depend on the stability of the material, available storage capacity, and so forth.

A1.1.3 Obtain the validation reference material(s) and store them under conditions that will ensure essentially no degradation of the critical property accepted reference value once it is established.

A1.1.4 Commercial standard reference materials are often available for use as a designated validation reference material. The property and the accepted reference value are available from the supplier.

A1.2 When commercial standard reference material is not available, the validation standard may be prepared from on-site process or product material meeting the desired specifications. Utilization of this type of material requires testing by a primary test method, preferably under reproducibility conditions, to establish the accepted reference value of the selected property.

A1.2.1 Collect and store the appropriate quantity of an on-site process or product material for use as a validation standard. Prepare and fill the necessary number of individual containers of validation standard for primary test method analyses to determine the ARV or SAV of the desired property.

A1.2.2 For each validation standard, obtain a minimum of ten primary test method results.

A1.2.2.1 More than ten primary test method results can be necessary to provide an average value having acceptable confidence limits. This can vary significantly for different primary test methods and validation standard properties.

A1.2.2.2 The controlling factors in defining the number of test results required are: degree of precision desired, testing costs, precision of the primary test method, and the criticality of the analyzer system accuracy and precision.

A1.2.3 For guidance in determining the number of primary test method results required to establish desired confidence limits for the ARV or SAV of the validation standard, refer to instructions provided in A1.4.

A1.2.4 To establish an ARV, it is necessary that the primary test method results be obtained under reproducibility conditions, to minimize effects of inter-laboratory bias and test variability.

A1.3 To establish an SAV, it is recommended that different operators and apparatus combinations be utilized to the maximum extent possible so the data are representative of site precision conditions.

A1.3.1 If it is considered necessary to obtain the multiple determinations in a single laboratory that has only one piece of apparatus available, make the multiple determinations over an extended period of time using multiple operators and testing other samples between the validation standard measurements. This approach will provide data obtained in a manner that is closest to site precision conditions.

A1.3.2 If the validation standard primary test method results are determined in a single laboratory, it is recommended that the laboratory maintain records verifying their bias status, based on participation in an industry-wide round-robin exchange sample testing program.

A1.4 *Calculating the Accepted Reference Value (ARV) or Site Assigned Value (SAV) for the Validation Reference Material*:

A1.4.1 Tabulate the primary test method results for the validation standard and visually screen for extreme values or outliers, or both, by an accepted statistically based rejection criterion.[8] Remove the outliers to further analyze the data. No more than 10 % of the data points should be removed through this process.

A1.4.2 Determine the arithmetic average (X_r) and the variance (S_r^2) of the acceptable validation standard data.

A1.4.2.1 Calculate the arithmetic average value using the following equation:

$$\bar{X}_r = \frac{\Sigma X_r}{N_r} \tag{A1.1}$$

where:

X_r = individual test results on the validation standard, and
N_r = number of test results.

A1.4.2.2 Calculate the variance by either of the following equations:

$$S_r^2 = \frac{\left[\Sigma X_r^2 - \frac{(\Sigma X_1)^2}{N_r}\right]}{(N_{r-1})} \tag{A1.2}$$

$$S_r^2 = \frac{\Sigma(X_r - \bar{X}_r)^2}{(N_r - 1)} \tag{A1.3}$$

[8] Supporting data are available from ASTM International Headquarters. Request RR: D02–1481.

A1.4.3 Compare the calculated validation standard data variance to that used to establish the reproducibility precision statement of the applicable primary test method. The statistical criteria for this judgment is the *F*-Test, which requires determination of the ratio of the variances as follows:

$$F = \frac{S_r^2}{\sigma_t^2} \quad \text{(A1.4)}$$

where:
S_r^2 = variance of validation standard data,
σ_t = historical reproducibility standard deviation of the primary test method.

A1.4.3.1 This standard deviation can be obtained by dividing the reproducibility (*R*) given in the precision statement of the primary test method by 2.772.

A1.4.4 Determine the limiting *F* value from the statistical *F* Distribution (5 % error level) tables for (N_r − 1) degrees of freedom in the numerator and 30 degrees of freedom in the denominator. (See Table A1.1 for a condensed portion of the *F* Distribution table.

A1.4.5 Compare the calculated *F* value to the limiting *F* value obtained from the *F* Distribution table and interpret as follows:

A1.4.5.1 If the calculated *F* value is equal to or less than the limiting *F* value, the variance of the validation standard data is not significantly worse than that of the expected primary test method precision and the validation standard data are qualified and acceptable.

A1.4.5.2 If the calculated *F* value is larger than the limiting *F* value, the variance of the validation standard data is not as good as the expected primary test method precision and the difference is statistically significant.

A1.4.6 When a significant difference between the variances occurs, the reason(s) for the substandard validation standard primary test method data requires investigation. Make any needed changes to the procedure or apparatus, or both, and then obtain a new set of validation standard primary test method data for comparison of the variances once again. Repeat the process until the precision of the primary test method data is acceptable.

A1.4.7 Assign the accepted reference value (ARV) and appropriate confidence limits for the property of the validation standard material tested as follows:

A1.4.7.1 Use the arithmetic average result of the validation standard primary test method data as the property ARV.

A1.4.7.2 Calculate the 95 % confidence interval limits for the ARV based on the validation standard test data using the following equation:

$$95\ \%\ \text{confidence limits} = X_r \pm t\frac{S_r}{\sqrt{N_r}} \quad \text{(A1.5)}$$

Where: *t* = students *t* value for the 95th percentile from standard t-tables for n-1 degrees of freedom. (See Table A1.2 for a condensed portion of the t-table).

A1.4.7.3 If the confidence interval width (magnitude between the upper and lower confidence limits) is too far apart to be considered useful, mathematically increase *N* and recalculate until the desired confidence interval width is obtained. Proceed and collect the additional results to meet the increased *N* requirement.

A1.4.8 Confirm the validation standard accepted reference value at periodic intervals because storage conditions and the factors that affect the stability of the material can change with time. The analyzer system user best determines the frequency of confirmation.

TABLE A1.1 F-Distribution
Degrees of freedom for numerator

	1	2	3	4	5	6	7	8	9	10	12	15	20
1	161	200	216	225	230	234	237	239	241	242	244	246	248
2	18.5	19.0	19.2	19.2	19.3	19.3	19.4	19.4	19.4	19.4	19.4	19.4	19.4
3	10.1	9.55	9.28	9.12	9.01	8.94	8.87	8.85	8.81	8.79	8.74	8.70	8.66
4	7.71	6.94	6.59	6.39	6.26	6.16	6.09	6.04	6.00	5.96	5.91	5.86	5.80
5	6.61	5.79	5.41	5.19	5.05	4.95	4.88	4.81	4.77	4.74	4.68	4.62	4.56
6	5.99	5.14	4.76	4.53	4.39	4.28	4.21	4.15	4.10	4.06	4.00	3.94	3.87
7	5.59	4.74	4.35	4.12	3.97	3.87	3.79	3.73	3.68	3.64	3.57	3.51	3.44
8	5.32	4.46	4.07	3.84	3.69	3.58	3.50	3.44	3.39	3.35	3.28	3.22	3.15
9	5.12	4.26	3.86	3.63	3.48	3.37	3.29	3.23	3.18	3.14	3.07	3.01	2.94
10	4.96	4.10	3.70	3.48	3.33	3.22	3.14	3.07	3.02	2.98	2.91	2.85	2.77
11	4.84	3.98	3.59	3.36	3.20	3.09	3.01	2.95	2.90	2.85	2.79	2.72	2.65
12	4.75	3.89	3.49	3.26	3.11	3.00	2.91	2.85	2.80	2.75	2.69	2.62	2.54
13	4.67	3.81	3.41	3.18	3.03	2.92	2.83	2.77	2.71	2.67	2.60	2.53	2.46
14	4.60	3.74	3.34	3.11	2.96	2.85	2.76	2.70	2.65	2.60	2.53	2.46	2.39
15	4.54	3.68	3.29	3.06	2.90	2.79	2.71	2.64	2.59	2.54	2.48	2.40	2.33
16	4.49	3.63	3.24	3.01	2.85	2.74	2.66	2.59	2.54	2.49	2.42	2.35	2.28
17	4.45	3.59	3.20	2.96	2.81	2.70	2.61	2.55	2.49	2.45	2.38	2.31	2.23
18	4.41	3.55	3.16	2.93	2.77	2.66	2.58	2.51	2.46	2.41	2.34	2.27	2.19
19	4.38	3.52	3.13	2.90	2.74	2.63	2.54	2.48	2.42	2.38	2.31	2.23	2.16
20	4.35	3.49	3.10	2.87	2.71	2.60	2.51	2.45	2.39	2.35	2.28	2.20	2.12
∞	3.84	3.00	2.60	2.37	2.21	2.10	2.01	1.94	1.88	1.83	1.75	1.67	1.57

TABLE A1.2 Table of *t* at 5 % Probability Level

Degrees of Freedom (*N*-1)	*t*
1	12.706
2	4.303
3	3.182
4	2.776
5	2.571
6	2.447
7	2.365
8	2.306
9	2.262
10	2.228
11	2.201
12	2.179
13	2.160
14	2.145
15	2.131
16	2.120
17	2.110
18	2.101
19	2.093
20	2.086