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Standard Test Method for Physical Integrity Testing of Single-Use Systems[1]

This standard is issued under the fixed designation E3336; 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 The test methods described in this standard are applicable for single-use manufacturing equipment, further called Single-use Systems (SUSs), used for (bio)pharmaceutical products.

1.2 The test methods described in this standard are not intended to be used on single-use technology for primary containers, combination products (products composed of any combination of a drug, device, or biological product), or devices. Appropriate procedures related to these products are discussed in documents covering the integrity assurance for primary containers (**1**)[2] or medical products (**2-4**).

1.3 The test methods and their validation are described to only cover testing of empty and dry SUSs. Residual liquid in the SUS can impact the test reliability and reproducibility.

1.4 The test methods are intended to be used to confirm the barrier properties of the test article, further called integrity testing, or test the SUS for leaks of certain sizes, further called leak testing.

NOTE 1—To verify that an integrity test can confirm the intended barrier properties of the SUS, its detection limit must be equal or better than the respective maximum allowable leakage limit.

1.5 The physical test methods covered by this standard are:

1.5.1 Pressure-based test methods.

1.5.2 Tracer gas-based test methods.

1.6 The physical test methods described are in general non-destructive and allow further use of the SUS.

NOTE 2—Some variations can be used in a destructive way, for example, to perform root cause analysis of the leak.

1.7 The standard describes the test apparatuses, operation procedures, environment requirements, and discusses specific challenges with testing SUSs, as well as how to perform robust validation of the test method.

1.8 This standard does not include methods to determine the maximum allowable leakage limit for maintaining the barrier properties of the SUS. For that, refer to Practice E3244 and Test Method E3251.

1.9 This standard does not describe how to select the appropriate test method. For that, refer to Practice E3244.

1.10 Furthermore, it does not discuss whether an integrity test should be conducted, at what frequency and where in the life cycle of a SUS. For that refer to Practice E3244.

1.11 Filter membrane integrity testing that additionally tests the integrity of the SUS is excluded from the scope. Certain components of the SUS may require additional testing.

1.12 *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, health, and environmental practices and determine the applicability of regulatory limitations prior to use.*

1.13 *This international standard was developed in accordance with internationally recognized principles on standardization established in the Decision on Principles for the Development of International Standards, Guides and Recommendations issued by the World Trade Organization Technical Barriers to Trade (TBT) Committee.*

2. Referenced Documents

2.1 *ASTM Standards:*[3]

E3244 Practice for Integrity Assurance and Testing of Single-Use Systems

E3251 Test Method for Microbial Ingress Testing on Single-Use Systems

F2095 Test Methods for Pressure Decay Leak Test for Flexible Packages With and Without Restraining Plates

F2338 Test Method for Nondestructive Detection of Leaks in Packages by Vacuum Decay Method

F2391 Test Method for Measuring Package and Seal Integrity Using Helium as the Tracer Gas

[1] This test method is under the jurisdiction of ASTM Committee E55 on Manufacture of Pharmaceutical and Biopharmaceutical Products and is the direct responsibility of Subcommittee E55.07 on Single Use Systems.

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

[3] 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.

2.2 *Other Documents:*

USP <1207> Sterile Product Packaging Integrity Evaluation, United States Pharmacopeia (USP), 2016

EU GMP, Annex 1 Manufacture of Sterile Products, European Commission, 2009

EU GMP, Annex 2 Manufacture of Biological Medicinal Products for Human Use, European Commission, 2018

USP <1> Injections and Implanted Drug Products (Parenterals) – Product Quality Tests, United States Pharmocopeia (USP), 2020

3. Terminology

3.1 *Definitions:*

3.1.1 *apparatus, n*—a technical equipment or machinery needed for leak or integrity testing purposes.

3.1.2 *balanced pressure drop, n*—the pressure drop of positive control articles balanced against the pressure drop of negative control articles; for analyzing the validation results, once this value turns into positive it means that a defective test article can be differentiated from a non-defective one.

3.1.2.1 *Discussion*—The pressure drop values are mean values of all test articles used for the validation, and include, depending on the quality requirements of the test validation, a defined number of standard deviations. In addition, the accuracy of the measurement instrument should be taken into consideration.

3.1.3 *bioprocess container (biocontainer), n*—a container (bag, bottle, tank, etc.) used primarily for liquid (or frozen liquid) storage during various stages of biopharmaceutical manufacturing processing.

3.1.4 *calibrated leak, n*—a hole which is characterized by its size (for example, artificially created into a SUS, a SUS's material, or component and used for creating positive controls).

3.1.4.1 *Discussion*—Often, the size is a nominal size which is equivalent to a gas flow through an idealized geometry (**1**). A commonly used idealized geometry is the "nominal diameter orifice size", corresponding to the size of a perfect circular hole of negligible length that would give the same gas flow in the calibration conditions (for example, dry air flow rate measured at 25 °C, with 1 bar_g inlet pressure and 1 atm outlet pressure).

3.1.5 *destructive test method, n*—a test method that will alter the intended use of the test article during the test and not allow further use (see also *non-destructive test method*).

3.1.6 *end user, n*—a company processing (bio)pharmaceutical products.

3.1.7 *family approach, n*—an approach to validate only one set of test parameters for a combination of several test article designs.

3.1.8 *hardware support structure, n*—a hardware that mechanically supports the SUS.

3.1.8.1 *Discussion*—This can be a restraining hardware, for example, a pair of plates or grids of rigid material, for example, aluminum or stainless steel, that are used to restrict the inflation of the SUS, or a hardware that does not restrict the inflation of the SUS to its nominal volume.

3.1.9 *integrity assurance, n*—a holistic approach of risk analysis and mitigation by means of product and process robustness, quality, and process control and integrity testing to assure that a SUS maintains its integrity prior to and during use.

3.1.10 *integrity test, n*—a test used to confirm the defined barrier properties of a SUS.

3.1.11 *leak, n*—a breach in a SUS's material or a gap between SUS's components through which there is a breakdown of the barrier property of interest.

3.1.12 *leak test, n*—a test used to identify leaks not correlated to the defined barrier properties of a SUS.

3.1.13 *maximum allowable leakage limit, n*—the greatest leakage rate (or leak size) tolerable for a given product package to maintain its barrier properties under its use-case conditions (for example, prevent any risk to product safety, product quality, or operator and environmental safety).

3.1.13.1 *Discussion*—In this test method's context, the product package is a SUS containing a (bio)pharmaceutical product, but not a final dosage form.

3.1.14 *negative controls, n*—the negative control articles are intact, under intended use-case conditions non-leaking SUS (see also *positive control*).

3.1.15 *non-destructive test method, n*—a test method that maintains the test article in a condition for further use, without impacting its quality attributes (see also *destructive test method*).

3.1.16 *positive controls, n*—the positive control articles are test articles of the exact same design as the negative control articles, equipped with a calibrated leak of known size (see also *negative control*).

3.1.16.1 *Discussion*—Positive controls can be manufactured by including a calibrated leak into the SUS or by attaching it using an appropriate connection.

3.1.17 *single-use components, n*—parts used in single-use systems, most commonly, but not limited to, bioprocess containers, tubing, connectors, clamps, valves, sensors, and filters.

3.1.18 *single-use system (SUS), n*—process equipment used in (bio)pharmaceutical manufacturing, disposed of after use and usually constructed of polymer-based materials.

3.1.19 *SUS supplier, n*—a manufacturer that produces and/or assembles single-use systems, also known as a system integrator.

3.1.20 *tracer gas, n*—a gas to be detected against the background of all other gases.

3.1.21 *tracer gas calibrated leak standard, n*—element emitting a known flow of tracer gas, used to calibrate tracer gas leak detectors. It is an assembly of a pressurized reservoir with an isolation valve and an orifice.

3.2 *Abbreviations:*

3.2.1 *BPOG*—Biophorum

3.2.2 *BPSA*—Bio Process Systems Alliance

3.2.3 *cGMP*—current Good Manufacturing Practice

3.2.4 *CQA*—critical quality attributes

3.2.5 *HLD*—helium leak detector

3.2.6 *ICH*—International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

3.2.7 *LoD*—limit of detection

3.2.8 *MALL*—maximum allowable leakage limit

3.2.9 *QbD*—quality by design

3.2.10 *QRM*—quality risk management

3.2.11 *SUS*—single-use system

3.2.12 *SUSI(T)*—single-use system integrity (testing)

3.2.13 *SUT*—single-use technologies

3.2.14 *TGD*—tracer gas detector

4. Significance and Use

4.1 The test methods outlined in this standard allow for suppliers and end users of SUSs in (bio)pharmaceutical manufacturing processes to detect a leak and/or confirm the barrier properties of empty, clean, and dry SUSs. Performing integrity testing can be a significant contribution to the overall integrity assurance of SUSs.

4.2 The two types of physical test methods outlined in this standard are:

4.2.1 Section 5, Pressure-Based Test Methods.

4.2.2 Section 6, Tracer Gas-Based Test Methods.

NOTE 3—Other test methods are currently being adapted for robust, reliable, and reproducible testing SUS, for example, Vacuum Decay Test Method as described in Test Method F2338.

4.3 Pressure-based test methods are generally less sensitive compared to tracer gas-based test methods but have a lower complexity and cost. To assist in selecting a method that will fit an application, refer to Table 1 in Practice E3244 for a more detailed comparison of the two methods.

4.4 Both types of test methods can be used to detect leaks of any sizes in a SUS (referred to as leak testing) or confirm the barrier properties of the SUS (referred to as integrity testing).

4.5 To ensure that integrity testing performed on SUSs is effective and accurate, the properties of the SUS (pressure capabilities, volume, material properties, etc.) must be considered. Also, a validation should be performed on the chosen test method as further described in 5.11 and 6.11.

4.6 Practice E3244 should be referenced to determine the maximum allowable leakage limit for a SUS, along with the routine testing requirements that are suitable for each application.

4.7 The purpose of the described test methods is not to stress the SUS until a potential defect occurs. The testing parameters, mainly test pressure, are independent from the use-case conditions. The robustness of the SUS under use-case conditions should be proven during product qualification.

4.8 This standard test method describes the test method principles, the apparatus designs, and method validations. For more detailed visualization of test setups and tested SUS designs, refer to Practice E3244 and more illustrative technical guides (**5**).

5. Pressure Based Test Methods

5.1 *Test Methods Principles:*

5.1.1 The basic principle of a pressure test is to detect leaks in the SUS by applying a defined pressure with air (or sometimes a specified gas).

5.1.2 The flow of gas through any leaks in the SUS can be detected either by a pressure decay method after isolation of the supply pressure or by direct flow measurement at a constant system pressure using suitable equipment upstream of the test article.

5.1.3 Both pressure decay and flow measurement tests depend on the ideal gas law (see Note 4) PV=nRT.

NOTE 4—PV=nRT with P: Pressure, V: Volume, n: Number of moles, R: Ideal gas constant, T: Absolute temperature.

5.1.4 Higher pressure, lower test volume and longer test time enhance sensitivity, while constant temperature and minimal ambient air convection is required during the test. However, pressure ratings of the test article should not be exceeded. Viscoelasticity and gas permeation characteristics should be considered.

NOTE 5—By using hardware support structure to mechanically support the SUS during the test, it might be possible to apply a test pressure above the pressure rating. Furthermore, specific components with limited pressure resistance (for example, membranes of single-use pressure sensors) must be protected against over pressurization.

NOTE 6—In order to enhance the test method sensitivity, for complex SUS designs it might be useful to separate the test article into several parts (for example, by clamping the tubing) and test these parts individually. This could also allow for testing individual parts with a higher pressure than other ones.

5.1.5 In the following sections, statements related to the term pressure decay are synonymous for flow rate.

5.2 *Apparatus:*

5.2.1 A measuring instrument that provides the following:

5.2.1.1 A sensor to detect pressure changes with sufficient sensitivity to detect theoretical leak rates according to the specification of the leaks to be detected in the SUS.

5.2.1.2 A timer to control pressurization of the SUS to a pre-set pressure, stabilize the pressure for a set time, and provide a time period during which pressure change is recorded.

5.2.1.3 A means to set pressure.

5.2.1.4 A means of holding and displaying the pressure change inside the SUS between begin and end of the test cycle.

5.2.1.5 A means (optional) to set pressure decay limits for a test recipe and alert the operator if the limit is exceeded.

5.2.1.6 A means to connect the test article in a leak tight manner, so that an inflation pressure can be applied to the SUS and changes in internal pressure can be sensed.

NOTE 7—It is important to verify the tightness of the entire testing device, so that it does not contribute to the pressure changes sensed during testing. For example, this can be done by doing one test without the test article connected.

5.2.1.7 A means (optional) to detect and avoid overpressurization potentially caused by a malfunction of the apparatus, that could lead to rupture of the SUS.

5.2.2 A hardware support structure (optional) that mechanically supports the test article when fully inflated or restricts its inflation that provides the following:

5.2.2.1 Sufficient pressure resistance to not damage the support structure when the pre-set test pressure is applied on the SUS.

5.2.2.2 A structured surface in contact with the test article allowing gas escape through a potential leak to avoid masking a leak in the supported surface area of the test article.

NOTE 8—Alternatively, a porous layer can be used between the surface of the SUS and the hardware support structure to allow sufficient gas escape through the potential leak. The effectiveness of this structured surface or porous layer should be confirmed during the leak test validation. When selecting appropriate material as a porous layer, the mesh width and the wire diameter should be considered as critical parameters that have an impact on the probability of detection. Re-use of the porous layer as well as the impact on further processing steps (for example, heat transfer) should be evaluated.

NOTE 9—The hardware support structure can be adjustable (optional) to optimize the volume of the test article.

5.3 *Challenges and Potential Interference:*

5.3.1 As pressure is a function of temperature, environmental conditions, especially temperature fluctuations, can have a significant impact on the pressure drop measurement. Therefore, the apparatus and the test article should not be placed in areas facilitating immediate temperature changes, for example, close to a window subjected to direct sunlight or close to an air conditioner.

5.3.2 A drift in pressure drop reading can also occur due to temperature changes of the test gas. Therefore, it is recommended to use test gas at the same temperature as the testing environment.

5.3.3 As pressure is a function of volume, flexibility of polymeric material can result in a volume change of the test article during the test and therefore impact the pressure drop measurement. It is recommended to choose a stabilization time sufficient to compensate for these expansion processes.

5.4 *Sampling, Test Articles, and Test Units:*

5.4.1 The sample quantity for a method validation is chosen to permit an adequate determination of representative performance. Positive and negative controls should be used to define the acceptance criteria.

5.4.2 The sample quantity for routine testing (for example, statistical or 100 % testing) should be based on a QRM approach, as described in Practice E3244.

5.4.3 Unique sample identification should be made prior to testing to allow the operator to refer to specific test articles, if necessary. Information such as test results and anomalies should be traceable to individual articles.

5.4.4 The identical SUS design should be used for method validation as to be used in the routine testing.

NOTE 10—A family approach is possible with testing the extremes of each family. Discussion on how to define appropriate families is provided in Appendix X1.

5.4.5 The identical apparatus and setup should be used for method validation as to be used for routine testing.

5.5 *Preparation of Apparatus:*

5.5.1 The apparatus should be placed in a temperature stable environment (for example, not close to air conditioning or direct sunlight) to avoid any drift in the pressure reading during the test. Limits for environmental influencing factors should be assessed during validation of the test method as described in 5.7.2.6.

5.5.2 The measuring instrument should warm-up after switch-on to reach a constant apparatus temperature during operation.

5.5.3 Connect the measuring device to compressed gas supply. Gas supply must be oil-free, dry, and free of particulates. This gas supply must be sufficient to maintain adequate and stable test pressure.

NOTE 11—Some measuring devices may have a built-in air compressor as gas supply. However, requirements on the test gas remain the same.

5.5.4 Surfaces of a potential hardware support structure should be clean and dry.

5.5.5 Apparatus should be checked to be leak tight according to 5.2.1.6.

5.6 *Validation of Test Method:*

5.6.1 For non-destructive testing, the absence of impact of the test on the CQA of the SUS must be validated.

5.6.2 The test method must be validated as a limit test using positive and negative control articles following result interpretation as described in 5.11.

5.6.3 Following elements are key parameters to be covered by the method validation:

5.6.3.1 the test pressure,

5.6.3.2 the stabilization time,

5.6.3.3 the test time.

5.6.4 To use the method as a limit test, following considerations should be evaluated during method validation:

NOTE 12—Most of these considerations are derived from ICH Q2 (R1) and USP <1207.1> requirements. Additional ones are derived from usual statistical analysis of a binomial distribution. For quantitative tests, please refer to ICH Q2 (R1) and USP <1207.1> requirements.

5.6.4.1 Accuracy: it corresponds to the percentage of test articles correctly classified.

5.6.4.2 Recall: sometimes called “sensitivity” of the test. It corresponds to the number of positive controls correctly classified divided by the total number of positive controls; when the test method is used as an integrity test, it is very important to set the acceptance limit at a level maximizing the recall, for obvious reasons, even if it impacts the precision.

5.6.4.3 Precision: it corresponds to the number of test articles correctly classified in the population of rejected test articles (classified as fail).

5.6.4.4 Repeatability: is verified by applying the test method on multiple sampling of the same homogeneous sample population, using the same testing conditions (same operator, limited period of time, same instrument); it is important to perform this test on a sufficient quantity of samples.

5.6.4.5 Ruggedness: is verified, if relevant, by having different operators performing the test, having the test performed at different days and using different instruments to perform the test.

5.6.4.6 Specificity: corresponds to the ability of the method to provide adequate differentiation between true negative and true positive test articles, despite potential interfering factors. Examples of potential interfering factors are described in 5.3.

5.6.4.7 The validation should be performed by testing a mix of positive and negative samples in random order.

5.6.4.8 Reproducibility, comparing the output of different labs, is generally out of scope of such validation.

5.6.5 The validation report should ideally include all the above elements, plus a detailed description of how the positive samples were made, how the defects present in the positive controls were calibrated or certified, and what are the elements considered to define the most severe cases of the validated space.

5.6.6 System suitability (also known as performance verification test) can be performed at the beginning and end of each testing sequence for added method assurance. Especially, probabilistic test methods may require a routine demonstration that the operator is able to successfully differentiate test articles without defect from those with leaks (ranging in size from smallest to largest, located at various positions), in a blinded challenge study.

5.7 *Calibration:*

5.7.1 The measuring instrument should be calibrated and qualified for its use.

5.7.2 To achieve a robust and reliable test method, and to eliminate as many interference as possible, the method validation should be done considering the following steps.

5.7.2.1 To eliminate material and configurations-specific interference (for example, creeping of the material) negative controls, meaning integral SUS, should be tested to establish a baseline reading for non-defective SUS.

5.7.2.2 To define the method sensitivity positive controls, meaning intentionally compromised SUS with a calibrated leak of a known size, should be tested to establish the reading for defective SUS.

NOTE 13—Calibrated leaks could, for example, be laser-drilled holes, glass capillaries, or microtubes. Leak sizes should be stated normalized in nominal diameter orifice size or leak rate.

NOTE 14—To confirm the effectiveness of the structured surface or porous layer, if used, the calibrated leak must be placed at the worst-case location for potential leak masking.

5.7.2.3 A family approach can be used to validate a broad range of different configurations. In this case, the extremes of each family should be used as positive and negative controls to validate the parameter set.

NOTE 15—Rationales to define the extremes of families is discussed in Appendix X1.

5.7.2.4 Depending on the required level of assurance, statistical calculation with mean values and standard deviations (for example, mean ± 3σ) should be applied on the test results, for positive and negative controls respectively.

5.7.2.5 The acceptance criteria for test evaluation should be placed in between these two set of curves and not interfere with the lowest value of the statistics for positive controls and highest value for statistics of the negative controls.

NOTE 16—More detailed information on statistical calculation and choice of acceptance criteria is provided in 5.11.

5.7.2.6 Recording of environmental conditions (for example, temperature, atmospheric pressure variation) during method validation should be done and appropriate limits should be derived as pre-requisite for routine testing.

5.8 *Reagents and Materials:*

5.8.1 Compressed air – supply cylinder and regulator.

5.8.2 Nitrogen (nominally 100 %) Gas – supply cylinder and regulator.

5.8.3 For SUS that will be further sterilized, and that are subjected to a non-destructive routine testing (test on SUS before use in biopharma manufacturing), following elements must be considered:

NOTE 17—This situation corresponds typically to a test performed by the SUS manufacturer, at the end of the assembly step.

5.8.3.1 Grade of the gas supply: equivalent to high purity (>99.99 %) or medical grade, with certificate of conformity; remaining gases are other gases that naturally can be found in air, at an equal or lower concentration.

5.8.3.2 Filtration of the gas supply, to address the risk of particulate matter.

NOTE 18—Particulates could also cause malfunction of the apparatus, for example, a built-in calibrated leak for calibration could be blocked.

5.8.4 For SUS that are sterile, and that are subjected to a non-destructive routine testing, following elements must be considered:

NOTE 19—This situation corresponds typically to a test performed by the end-user, before using the SUS in the drug manufacturing process.

5.8.4.1 Gas supply must be compliant to regulatory requirements, for its production and its monitoring. This includes performing periodically a microbial monitoring of the gas at point of use.

5.8.4.2 Filtration of the gas supply, with a sterilizing gas filter, to maintain the sterility of the SUS and address the risk of particulate matter.

5.9 *Conditioning:*

5.9.1 Test article should be conditioned to obtain the same temperature conditions as exist for the test apparatus. Since measured pressure change is also a function of temperature, then the test articles must be at a stable temperature. Testing should be done under typical SUS manufacturing environment conditions. All conditions should be recorded at the time of the test.

NOTE 20—As seen in the combined gas laws, the pressure change is a function of temperature. Test articles and the test gas should be at similar temperatures.

5.10 *Procedure:*

5.10.1 *Test Article Preparation*—As residues in the SUS could block a potential leak, the SUS should be tested empty, clean, and dry. In case of testing a pre-sterilized SUS, appropriate measures (for example, pressurizing the SUS through a sterilizing grade filter) must be taken to maintain the sterility.

NOTE 21—To maximize sensitivity of the test, the smallest internal volume of the SUS is desired. See Note 9 about the optional hardware support structure.

5.10.2 *Apparatus Preparation*—The apparatus should be prepared as described in 5.5. Appropriate test parameters should be defined according to 5.8.1.

5.10.3 Select and set the test pressure.

5.10.4 Select and set pressurization, stabilization, and test time.

5.10.5 Select and set pressure decay limits (if available).

5.10.6 Place the SUS in its hardware support structure (if available).

5.10.7 Connect the test article to the measuring instrument in a leak-tight manner.

NOTE 22—Depending on the complexity of the insertion into the hardware support structure and the connection to the measuring instrument, 5.10.6 and 5.10.7 can be done vice versa.

5.10.8 Begin the test by activating the timer controls and valves to inflate, stabilize, and measure the test pressure inside the SUS.

5.10.9 Observe the pressure decay at the end of the test time period and note if the pressure decay limit has been exceeded.

NOTE 23—Choice of times depends on test article variables and leak rate requirements. For example, small changes in initial test pressure may occur from flexible package stretch, thus slightly increasing its volume (decreasing its pressure) or from fixture contact or the expanding gas medium. Increased stabilization time will allow these effects to become stable before the test data period begins. Test times are selected based on required leakage rates or pressure decay criteria along with the SUS volume. See 5.11.1 for detailed explanation how to setup appropriate test parameters.

5.11 *Calculation or Interpretation of Results:*

5.11.1 For the validation of the test method mean values and standard deviations of the time-based pressure drop recording should be calculated and interpreted in the following way to find a suitable parameter set for a reliable and repeatable differentiation of defective from non-defective test articles.

5.11.1.1 *Negative Controls:*

(1) Mean values should not show a steep slope and significant pressure drop at the end of the test time. If the stabilization time is chosen appropriately pressure drop should remain close to zero.

(2) A significant pressure drop can be improved by increasing the stabilization time or it indicates a problem in the test setup.

(3) A significant negative pressure drop (pressure increase) indicates a problem with environmental testing conditions or malfunctioning testing device.

(4) The standard deviation can be much larger than the mean value, as the mean values should be close to zero.

(5) As defined in 5.7.2.4, the standard deviation multiplied to achieve the target confidence interval is added to the mean value (for example, for $\bar{x}_{neg} + 3\sigma_{neg}$ to achieve a final confidence interval of 6σ).

5.11.1.2 *Positive Controls:*

(1) Mean values should show a steep and continuous slope with a significant pressure drop at the end of the test time.

(2) An insignificant pressure drop can be improved by increasing the test time or test pressure. It can also indicate the test method's incapability to detect the selected leak size.

(3) Along the time-based recording the standard deviation should only be a fraction of the mean values, as the mean values should increase constantly.

(4) As defined in 5.7.2.4, the standard deviation multiplied to achieve the target confidence interval is subtracted from the mean value (for example, for $\bar{x}_{pos} - 3\sigma_{pos}$ to achieve a final confidence interval of 6σ).

5.11.1.3 Determining the acceptance limit by calculating the balanced pressure drop:

(1) To determine the acceptance limit, time-based statistical calculations as described in 5.11.1.1*(5)* and 5.11.1.2*(4)* have to be compared to calculate the balanced pressure drop.

(2) As all measurements for non-defective test articles as well as for the defective ones are subjected to the accuracy of the measurement instrument, twice the accuracy should be taken into consideration as the minimum gap between statistics of positive and negative controls for calculating the balanced pressure drop.

(3) As shown in Fig. 1, the minimum test time required to

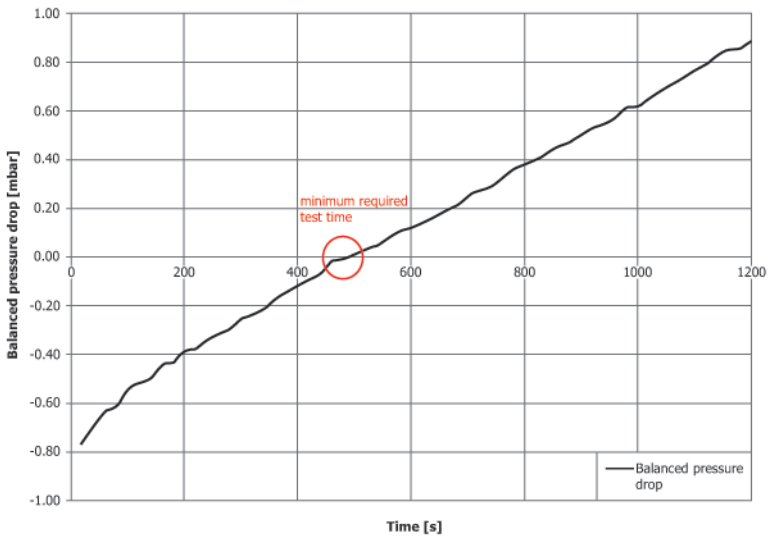

FIG. 1 Example of Balanced Pressured Drop With Selection of Minimum Test Time

reliably differentiate positive from negative controls is the point where the balanced pressure drop turns and remains positive (for example, $0 < (\bar{x}_{pos} - 3\sigma_{pos}) - (\bar{x}_{neg} + 3\sigma_{neg}) - 2*accuracy$[4]).

(4) As shown in Fig. 2, according to the calculation provided in 5.11.1.3*(3)* an acceptance limit for the maximum allowed pressure drop should be chosen at that point of test time that shows a clear differentiation between negative and positive controls.

5.11.2 For routine testing the obtained pressure drop at the end of the test time has to be compared to the acceptance criteria defined according to 5.11.1.

5.11.2.1 A pressure drop exceeding the acceptance criteria indicates a failed test and a SUS with a leak at least the size as chosen during the test method validation.

5.11.2.2 A pressure drop below the acceptance criteria indicates a passed test and a SUS with no leak or a leak of smaller size as chosen during the test method validation.

5.11.2.3 Unexpectedly high pressure drops can indicate an improper or leaking test setup. Make sure the test setup is leak tight according to procedure described in 5.2.

6. Tracer-Gas Based Test Methods

6.1 *Test Methods Principles:*

6.1.1 Leaks are detected by measuring the presence of a tracer gas entering or exiting the test article. The tracer gas detector (TGD) is measuring the quantity of tracer gas molecules, with calibration this is converted into a volumetric flow rate of the tracer gas.

6.1.2 Current standard provides detailed steps for test methods using helium as tracer gas. Other tracer gases can be used, providing adequate assessments are made to successfully cover the differences with helium.

6.1.3 Several leak detection methods are possible using TGD:

6.1.3.1 Spray test method – local detection (out-in): the test article is connected to the TGD and slowly challenged at the target points by a spray of tracer gas delivered from the outside with a spray pistol.

6.1.3.2 Sniffer test method – local detection (in-out): the test article is pressurized with the tracer gas and controlled from the outside at the target points by a test gas probe connected to the TGD.

6.1.3.3 Chamber gas enrichment test method – global detection (out-in): the test article is connected to the TGD and surrounded by an enclosure (flexible or rigid) that is filled with the tracer gas.

6.1.3.4 Chamber accumulation test method – global detection (in-out): the test article, placed in a test chamber, is pressurized with the tracer gas; the tracer gas leaving the test article accumulates in the test chamber and is measured with a sniffer probe after a defined time period.

6.1.3.5 Chamber vacuum test method – global detection (in-out): the test article, placed in a test chamber under vacuum, is pressurized with the tracer gas; the tracer gas leaving the test article is measured by the TGD connected to the test chamber.

6.1.3.6 Bombing test method – global detection (out-in): the test article is placed in a pressure vessel, filled with the tracer gas; it is left several hours in the pressure vessel, to let the test gas enter in the test article through leaks; the test article is then placed in a vacuum chamber connected to a TGD and the tracer gas flow escaping from the test article is measured, similarly to 6.1.3.5.

6.1.4 Amongst the above test methods, only the chamber test methods (6.1.3.3, 6.1.3.4, 6.1.3.5) and the bombing test method (6.1.3.6) can be qualified as deterministic, quantitative

[4] Accuracy of the measurement device as mentioned in 5.11.1.3*(2)*.

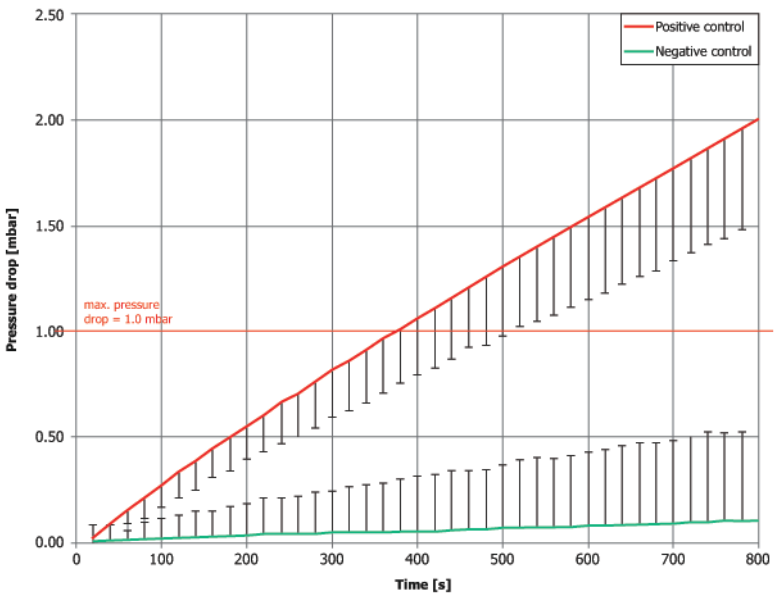

FIG. 2 Example of Acceptance Criteria Selection (1.0 mbar at 800 s test time)